



**Scientific Letter**

**Epidemiology and Clinical Characteristics of Henoch-Schönlein Purpura Associated with *Mycoplasma pneumoniae* Infection in 131 Children in Hubei Province, China**

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**To the editor.**

Henoch-Schönlein purpura (HSP) is the most common cause of vasculitis in children. The incidence of HSP in China is 8.13–14.06/100000 children.<sup>1,2</sup> The most challenging aspect of HSP is determining the specific trigger for leukocytoclastic vasculitis. Associations with bacterial and viral infection and immunisation have been reported.<sup>1,3,4</sup>

The most common cause of HSP is probably an infection of the respiratory tract.<sup>1-4</sup> *Mycoplasma pneumoniae* (MP) is a common bacterial pathogen causing *M. pneumoniae* pneumonia (MPP) in children. In China, the rate of MPP is 30.3% - 37.5% in paediatric patients aged from 1 month to 18 years.<sup>5</sup> Although there have been several case reports on MP-associated HSP, data on the aetiology and epidemiology of children with HSP and MP infection in developing countries are still insufficient.

The participants in this study were recruited from all patients between the ages of 2 and 15 years who were admitted to two hospitals in Hubei province, China, from January 2015 and December 2019. We evaluated the epidemiologic and clinical characteristics of those patients diagnosed with MPP and HSP and 131 HSP patients with MPP, an association that was rarely systematically described in the literature.

**Methods.**

**Patient selection.** Children with HSP, younger than 15 years old, were recruited for the present study between January 2015 and December 2019. The diagnosis of HSP was based on European League against Rheumatism endorsed consensus criteria for HSP classification.<sup>6</sup> Children with HSP, excluding infection as a trigger, were determined to serve as non-infectious cases for direct comparison, as well as for epidemiological interest. During the same period, children diagnosed with MPP, regardless of HSP, were also surveyed. The diagnosis of pneumonia was defined

as follows: clinical manifestations (fever, cough or wheezing), physical examination and chest imaging with infiltrates.<sup>7</sup> MPP is defined as pneumonia with MP infection, excluding other pathogen infections.

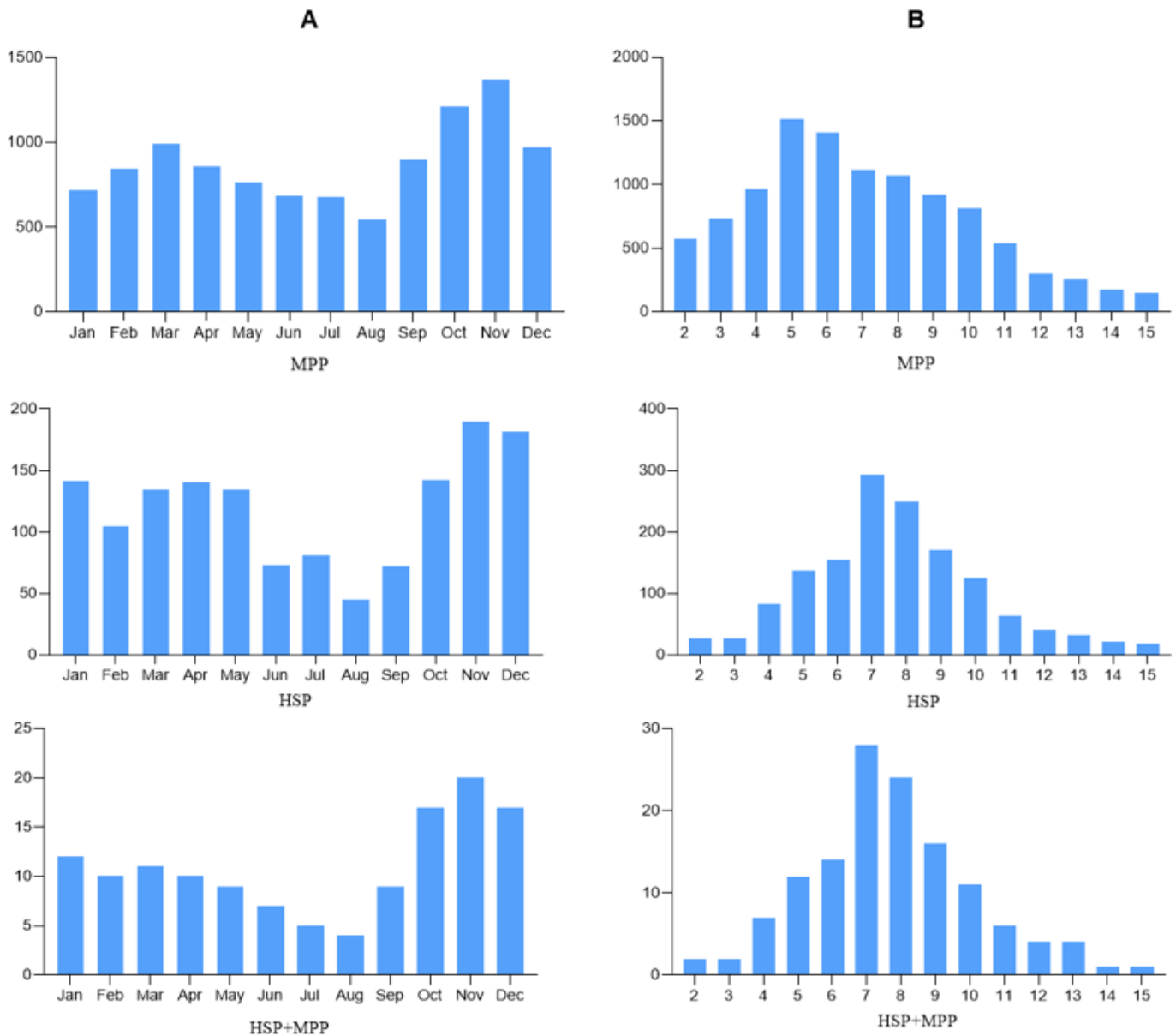
**Laboratory tests for MP infection.** MP antibodies were detected using the passive agglutination method (Serodia-Myco II, Fujirebio, Japan). Positive MP infection was defined as single titres of serum MP antibody  $\geq 1:320$  or seroconversion (increased antibody titres  $\geq 4$  fold).<sup>8</sup>

**Exclusion criteria.** (1) Patients with impaired immune function or who were receiving immunosuppressive therapy or were taking nephrotoxic drugs; (2) Patients who received blood transfusions or other blood product treatment in the past few months; (3) Patients with severe heart, liver, kidney or other organ system diseases; (4) Patients with chronic pulmonary disease that might affect the chest X-ray results, aspiration pneumonia or interstitial lung disease. (5) Patients with incomplete clinical data; (6) Patients with HSP associated with infections by other pathogens.

**Statistical analyses.** The statistical analyses were performed using SPSS ver. 21.0 software (SPSS, Inc., Chicago, IL, USA). Normally distributed continuous data are expressed as mean  $\pm$  standard deviation. Comparisons of the frequencies among groups were analysed using Chi-squared tests. Comparisons of mean values between groups were performed using the independent sample t-test. A P-value of less than 0.05 was considered statistically significant.

**Results.**

**Frequency of MP-triggered HSP.** Among the 1437 children with HSP, 131 children were diagnosed with MPP, and the incidence of MP-triggered HSP was 9.1% (131/1437).



**Figure 1. A.** Monthly or seasonal distribution of cases in HSP and MPP. **B.** Age distribution in HSP and MPP.

*Monthly or seasonal distribution of cases in HSP and MP infection.* In terms of seasonal frequency, MPP cases and HSP with MPP cases occurred mainly in the autumn and winter seasons. No differences were found in the reported years. All cases occurred less frequently in summer, and HSP cases occurred mainly in the winter (**Figure 1A**).

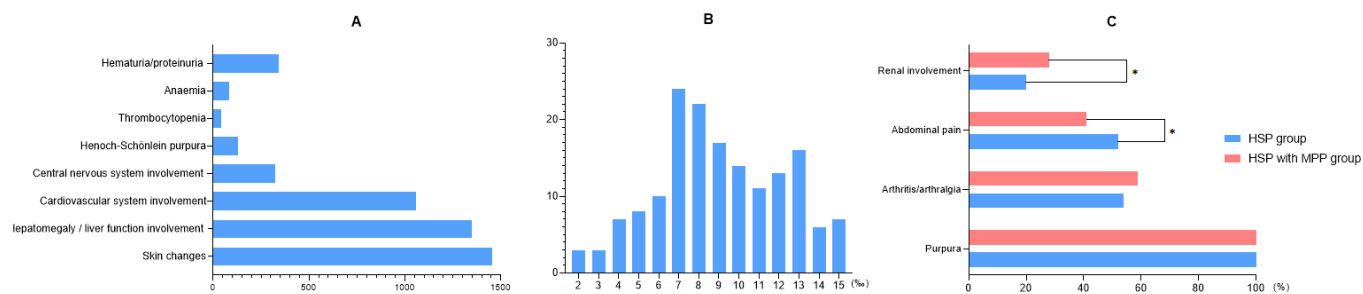
*Age distribution in HSP and MPP.* In terms of age distribution, a bell-shape distribution pattern with a peak prevalence mainly in the 4–10 years age range was observed in the HSP and HSP with MPP cases. However, the peak ages were slightly different across MPP cases (**Figure 1B**).

*Extrapulmonary manifestations of MPP.* During the same period, 10519 children with MPP were diagnosed, of which HSP accounted for 1.2% (131/10519) (**Figure 2A**). In cases of MPP, a significantly greater frequency

of MP-triggered HSP was found in different ages ( $\chi^2 = 39.340$ ,  $p < 0.001$ , **Figure 2B**).

*Clinical manifestations of HSP with MP infection.* In the non-infectious group, there were 716 cases with purpura (100.0%), 389 (54.3%) cases with arthritis/arthralgia, 373 (52.1%) cases with abdominal pain and 146 (20.4%) cases with renal involvement. MP-triggered HSP cases exhibited arthritis/arthralgia (77/131, 58.8%) most frequently, followed by abdominal pain (55/131, 42.0%) and renal involvement (37/131, 28.2%). Compared with the non-infectious group, infectious cases had a significantly higher frequency of renal involvement ( $\chi^2 = 4.032$ ,  $p = 0.045$ ) and a lower frequency of abdominal pain ( $\chi^2 = 4.528$ ,  $p = 0.033$ ) (**Figure 2C**).

*Therapeutic response.* The therapeutic response of the non-infectious cases compared with infectious cases is presented in **Table 1**. Significant differences were



**Figure 2.** A. Extrapulmonary manifestations of MPP. B. Age distribution in MPP with HSP. C. Clinical manifestations in HSP. \*,  $p < 0.05$ .

**Table 1.** Duration time (day) between non-infectious cases and MPP cases.

HSP group (n = 716)			HSP with MPP group (n = 131)			t	p
Clinical manifestations	Total cases	Duration (days)	Clinical manifestations	Total cases	Duration (days)		
Purpura	716	4.75 ± 1.73	Purpura	131	5.10 ± 1.86	2.129	0.034
Arthritis/arthralgia	389	2.61 ± 1.33	Arthritis/arthralgia	77	2.95 ± 1.40	2.043	0.042
Abdominal pain	373	2.75 ± 1.47	Abdominal pain	55	2.96 ± 1.58	1.005	0.315
Renal involvement	146	4.25 ± 1.94	Renal involvement	37	4.76 ± 2.42	1.356	0.177

observed in the duration of purpura ( $t = 2.129$ ,  $p = 0.034$ ) and arthritis/arthralgia ( $t = 2.043$ ,  $p = 0.042$ ) between the two groups.

**Discussion.** MP can cause milder upper respiratory tract infections (pharyngitis, sinusitis) and severe lower respiratory tract infections (bronchitis, pneumonia) and damage the extrapulmonary systems.<sup>8</sup> The majority of extrapulmonary symptoms are associated with skin changes such as exanthematous skin eruptions, urticaria, erythema nodosum, Stevens-Jonson syndrome and HSP. Data on the prevalence of MP infection in children with HSP are scarce. Timitilli et al.<sup>9</sup> investigated the extrapulmonary manifestations of 92 children with MP infection and found just one case with HSP. In the present study, 10519 children with MPP were diagnosed, of which HSP accounted for 1.2%.

MP stimulates the production of the interleukins and tumor necrosis factor  $\alpha$  and can cause vasculitis.<sup>10,11</sup> HSP is a leukocytoclastic vasculitis that affects small vessels. Clinical manifestations of HSP typically include rash, arthritis, and gastrointestinal and sometimes renal involvement. Immune complexes activate cytokines, parts of complement and directly influence the endothelium. MP was the common infectious agent identified by MP antibodies in 131 cases (9.1%) from 1437 HSP cases in our study. Moreover, 37 cases triggered by MP included renal involvement. Several previous studies have reported direct evidence of HSP caused by MP.<sup>11-13</sup>

It is known that the seasonality of HSP is determined by the factors of these triggers and that age distribution and manifestations vary.<sup>1</sup> The epidemiological characteristics of a disease can help determine the aetiological agents of the disease. For this reason, we evaluated and compared the epidemiological

characteristics among HSP, MPP and HSP associated with MPP in children. In terms of seasonal frequency, MPP cases and HSP with MPP cases occurred mainly in the autumn and winter seasons. All cases occurred less frequently in summer, and HSP cases occurred mainly in the winter. The epidemiological profiles in HSP with MP infection were similar to those with HSP. In terms of age distribution, a bell-shape distribution pattern with a peak prevalence mainly in the 4–10 years age range was observed in the HSP and HSP with MPP cases. However, the peak ages were slightly different across MPP cases (**Figure 1B**). In cases of MPP, a significantly greater frequency of MP-triggered HSP was found in different ages ( $p < 0.001$ ). Children might have distinct immune responses and clinical symptoms depending on their age.<sup>14</sup>

Compared with the non-infectious group, a significantly higher frequency of renal involvement in the infectious group ( $p = 0.045$ ) was noted. PCR and immunofluorescence failed to detect MP antigens in the renal parenchyma in a previous study. However, other reports have noted that failure to detect MP antigens does not necessarily rule out a role for this microorganism because the pathogenesis of postinfectious renal involvement is more likely to be based on immunologic mechanisms. An immune reaction to the glomeruli could be suggested by immunofluorescence detection of anti-MP antibodies in the glomeruli. The antigen involved could be mycoplasmal or a cross-reacting renal antigen.<sup>15</sup>

An objective of the present study was to explore the therapeutic response between non-infectious cases and infectious cases by analyzing the duration of the main clinical manifestations. Significant differences were observed in the duration time of purpura ( $p = 0.034$ ) and arthritis/arthralgia ( $p = 0.042$ ) between the two groups.

Although a higher frequency of renal involvement was noted, the differences in the duration of renal involvement do not attain statistical significance due to the limited number of participants enrolled. Treatment with macrolides led to remission of the disease.

**Conclusions.** We report 131 paediatric cases of HSP children MPP with prolonged skin and joint changes.

The incidence of MP-triggered HSP was 9.1%, while MPP in children with HSP was 1.2%. The epidemiological characteristics of HSP with MPP were similar to those of HSP in terms of age distribution and seasonal variations. We suggest that in cases of prolonged symptoms of vasculitis due to HSP, MP infection could be a potential cause of exacerbation of the disease.

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**Competing interests:** The authors declare no conflict of Interest.

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