Received: 11 February 2019 | Revised: 3 March 2019 | Accepted: 9 March 2019

DOI: 10.1002/jcla.22887

RESEARCH ARTICLE

WILEY

Impact of atopy on the severity and extrapulmonary manifestations of childhood *Mycoplasma pneumoniae* pneumonia

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Funding information
Funding support for this study was provided by the Tianjin Health Bureau Foundation of China (2014KZ049).

Objectives: The impact of atopy on disease severity and extrapulmonary manifestations in children with *Mycoplasma pneumoniae* (MP) pneumonia is unknown.

Methods: Patients diagnosed with MP pneumonia between January 2016, and December 2017, were enrolled in this study. A total of 150 MP pneumonia patients were enrolled at diagnosis and divided into the atopic group (n = 48) and the nonatopic group (n = 102). Furthermore, these patients were also assessed after being divided into the pulmonary group (n = 120) and the extrapulmonary group (n = 30). Clinical characteristics, respiratory disease severity, any allergy history, and specific allergen sensitizations were collected from all patients. The serum interleukin-17 (IL-17) and total immunoglobulin E (IgE) levels were also measured.

Results: More children in the atopic group than those in the nonatopic group presented with severe MP pneumonia, tachypnea, oxygen therapy, steroid treatment, atopic conditions including asthma attack, a previous history of asthma, decreased IL-17 levels, and increased IgE levels (all $P < 0.05$). When compared with those in the pulmonary group, the patients in the extrapulmonary group showed higher percentages of atopy, higher total IgE levels, and lower IL-17 levels (all $P < 0.05$).

Conclusions: Atopy may be a risk factor for disease severity and extrapulmonary manifestations in children with MP pneumonia.

KEYWORDS
atopy, extrapulmonary manifestations, interleukin-17, *Mycoplasma pneumoniae* pneumonia, severity

1 | INTRODUCTION

Mycoplasma pneumoniae (MP) is a common cause of community-acquired pneumonia (CAP), mainly in children and young adults, and it is well known for causing various respiratory and extrapulmonary diseases. However, the pathogenesis remains unclear. Recent evidence supports the fact that direct and indirect (immune-mediated) mechanisms have been described in MP infection, but the latter mechanisms have been mainly implicated in the extrarespiratory complications of MP infection.[1] At the same time, the participation of an excessive host immune response is also thought to be involved in the severity of MP pneumonia.[2]

Interleukin-17 (IL-17) is an important immune mediator during systemic immune reactions and is involved in the inflammatory response in

MP pneumonia.[3] In addition, IL-17 also plays a key role in autoimmune diseases.[4] Recently, it has been reported that the breakdown of the immune balance between T helper type 17 (Th17) cells and Tregs may be part of the process leading to the subsequent development of extrapulmonary manifestations.[5] These findings indicate that IL-17 may be involved in disease severity and extrapulmonary manifestations.

Mycoplasma pneumoniae has strong clinical associations with asthma exacerbations and morbidity in both children and adults. Total and specific IgE responses have been described during MP respiratory infections. Recently, Medina et al[6] reported that community-acquired respiratory distress syndrome (CARDS) toxin is a critical factor needed to elicit an important immunoglobulin E (IgE) response. Atopy refers to an inherited tendency to produce IgE antibodies in response to small amounts of common environmental proteins. Atopy can be present in the form of symptomatic sensitization to one or more allergens, which means that an individual with a confirmed allergic sensitization exhibits clinical allergy. Thus, a potential association between the category of reactive diseases caused by MP and atopy might be highlighted.

Recently, Dimitri Poddighe et al[7] observed an age-dependent significant increase in the serum IgE levels in five children with different extrarespiratory complications of MP infection, indicating the condition of atopy. Moreover, they also confirmed this observation in a wider cohort of children; in the extrapulmonary disease group, the total serum IgE levels were significantly higher than those in children with classic respiratory infections due to MP.[8] These observations suggest that atopy might be associated with MP-related extrarespiratory manifestations; however, the influence of atopy on extrarespiratory complications of MP infection is largely unknown. Another study suggested that atopy may be a risk factor for the presence and severity of refractory MP pneumonia,[9] but no further data have been available to indicate the effect of atopy on the severity of MP pneumonia.

In this study, we investigated clinical features, including respiratory disease severity, atopic conditions, and serum IL-17 and total IgE levels, in children with MP pneumonia to determine the impact of atopy on disease severity and extrapulmonary manifestations and assess the role of IL-17 and IgE in disease pathogenesis.

2 | METHODS

2.1 | Study subjects and design

A total of 150 children hospitalized with MP pneumonia were consecutively enrolled in this study at the Tianjin Integrated Traditional Chinese and Western Medicine and Tianjin Nankai Hospital of China between January 2016, and December 2017. The ages of the patients ranged from 3 to 14 years old. Patient characteristics, respiratory disease severity, extrapulmonary manifestations, any allergy history, and specific allergen sensitizations were recorded. This study was approved by the Research Ethics Committee of Tianjin Nankai Hospital (NKYY_YX_IRB_2018_029_01).

To estimate the influence of atopy on respiratory severity, the patients were divided into atopic and nonatopic group. The respiratory disease severity was evaluated on the basis of pleural effusion, tachypnea, cyanosis, oxygen requirements, steroid requirements, and mechanical ventilation. At the same time, the patients were also divided into an extrapulmonary group and a pulmonary group to evaluate the impact of atopy on extrapulmonary manifestations. Furthermore, the levels of IL-17 and IgE were compared between the atopic and nonatopic groups and between the pulmonary and extrapulmonary groups.

2.2 | Diagnosis of *Mycoplasma pneumoniae* pneumonia

Mycoplasma pneumoniae pneumonia patients were diagnosed based on their clinical presentation (such as fever, cough, dyspnea, and crackles) and radiological findings and the changes in their antimycoplasma antibody titers. The serum of patients was used to test antimycoplasma IgM antibody titers by the microparticle agglutination method using a commercial kit (Serodia-Myco II, Fujirebio, Tokyo, Japan). The antimycoplasma IgM antibody titers were regarded as positive when the titers were ≥1:160 in the admission phase or when the titers of IgG were over fourfold higher in the symptomatic recovery phase than in acute phase.[10,11]

At the same time, polymerase chain reaction (PCR) testing of respiratory secretions was performed to detect other pathogens, such as influenza viruses, parainfluenza viruses, human adenoviruses, and respiratory syncytial virus. If any of these assays for other pathogens were tested positive, the patients were excluded from this study. Furthermore, patients that entered the recovery stage of pneumonia after admission, as shown by a stable body temperature and improved chest X-ray findings, were excluded from this study. In addition, patients with asthma, recurrent respiratory tract infections, primary immunodeficiency, secondary immunodeficiency, or chronic lung disease were also excluded from this study.

2.3 | Identification of atopy

Routine laboratory tests were performed, including measurements of the white blood cell count, eosinophil count, C-reactive protein (CRP) level, total serum IgE level, and allergen-specific IgE antibody level. The total IgE concentration and levels of specific IgE specific for eight common aeroallergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat dander, dog dander, Alternaria, cockroaches, tree pollen mixture, and weed pollen mixture) were assayed using Immuno CAP(Pharmacia Diagnostics, Uppsala, Sweden). Atopy was defined as at least one specific IgE level >0.35 IU/mL.[12,13]

2.4 | Measurement of the serum IL-17 level

Venous blood was taken from each subject, centrifuged at 1000 × g for 10 minutes at 4°C, and stored at −80°C. The serum IL-17 level was measured by using commercial enzyme-linked immunosorbent assays (ELISAs) (DBD Inc, San Diego, CA, USA), according to the manufacturer's instructions. The sensitivity of this assay was 1.0 pg/mL.

2.5 | Statistical methods

All statistical analyses were performed using the SPSS 17.0 software package. The normal distribution of the values in each group was demonstrated by the Kolmogorov-Smirnov test. Quantitative variables are expressed as the means ± standard deviation (SD) or the median values with the interquartile range (IQR). Comparisons between the normally distributed parameters of two groups were made with unpaired *t* tests. The Mann-Whitney *U* test was used for the serum CRP and total IgE levels, which were not normally distributed. Categorical variables were compared between two groups by using the chi-square test. A *P*-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Comparisons of clinical and laboratory characteristics between atopic and nonatopic children with MP pneumonia

Of the 150 enrolled children with MP pneumonia, 77 were male and 73 were female. The patients had a mean age of 6.6 years (range 3-14 years). According to the atopy test results, 48 (32.0%) subjects were assigned to the atopic group, and the other 102 (68.0%) were assigned to the nonatopic group. Significantly greater proportions of patients with asthma attack and a previous history of asthma were observed in the atopic group compared with the nonatopic group (27.1% vs. 4.9% and 16.7% vs. 2.9%, respectively, all $P < 0.05$). However, there were no significant differences in age, gender, duration of hospitalization, types of pneumonia, allergic rhinitis, atopic dermatitis, or family history of allergic diseases between the two groups ($P > 0.05$, Table 1).

The atopic group had a significantly higher total serum IgE level than the nonatopic group (224.5 [115.5-402.3] IU/mL vs. 69.9 [38.9-150.8] IU/mL, respectively, $P = 0.000$). In contrast, the IL-17 levels were significantly lower in the atopic patients compared with the nonatopic patients (388.3 ± 190.6 pg/mL vs. 575.2 ± 149.5 pg/mL, respectively, $P = 0.000$). There were no significant differences in the white blood cell counts, eosinophil counts, or CRP levels (all $P > 0.05$, Table 1).

3.2 | Comparison of respiratory disease severity between atopic and nonatopic children with MP Pneumonia

Thirty-three (68.8%) subjects in the atopic group developed severe MP pneumonia, which was more than the number that developed

TABLE 1 Comparison of clinical and laboratory characteristics between atopic and nonatopic children with MP pneumonia

	Atopy	Nonatopy		
	n = 48	n = 102	Test	*P*-value
Demographics				
Age (y)	6.1 ± 2.6	6.9 ± 2.7	−1.959	0.052
Gender(M/F)	24/24	53/49	0.050	0.823
Duration of hospitalization (d)	9.0 ± 2.3	8.4 ± 2.0	1.718	0.088
Type of pneumonia, n (%)			0.483	0.487
Bronchopneumonia	32 (66.7)	62 (60.8)		
Lobar pneumonia	16 (33.3)	40 (39.2)		
Asthma attack, n (%)	13 (27.1)	5 (4.9)	15.208	0.000
Previous history of asthma, n (%)	8 (16.7)	3 (2.9)	7.142	0.008
Allergic rhinitis, n (%)	7 (14.6)	10 (9.8)	0.742	0.389
Atopic dermatitis, n (%)	9 (18.8)	13 (12.7)	0.940	0.332
Family history of allergic diseases, n (%)	6(12.5)	7 (6.8)	0.695	0.404
Laboratory				
White blood cell (×/μL)	7255.5 ± 3189.1	7442.9 ± 3201.0	−0.335	0.738
LogTEC(×/μL)	2.3 ± 0.2	2.3 ± 0.3	0.108	0.914
CRP (mg/L)	8.0 (1.9-28.1)	11.1 (2.5-23.7)	−0.785	0.433
Total IgE(IU/mL)	224.5 (115.5-402.3)	69.9 (38.9-150.8)	−5.288	0.000
IL-17(pg/mL)	388.3 ± 190.6	575.2 ± 149.5	−5.983	0.000

CRP, C-reactive protein; IL-17, interleukin-17; LogTEC, logarithmic transformation of total eosinophil count; MP, *Mycoplasma pneumoniae*.

severe MP pneumonia in the nonatopic group (68.8% vs. 11.8%, respectively, $P = 0.000$). Significantly greater proportions of patients with tachypnea, oxygen therapy use, and steroid therapy use were also observed in the atopic group compared with the nonatopic group ($P < 0.05$, Table 2). Furthermore, the atopic group had a markedly longer duration of steroid therapy than nonatopic group (5.4 ± 1.9 days vs. 3.9 ± 1.2 days, respectively, $P = 0.002$). However, none of the patients experienced organ failure, required mechanical ventilation, or died (Table 2).

3.3 | Extrapulmonary manifestations of MP pneumonia

As shown in Table 3, there were skin manifestations in 36.7% of the patients. Of all children, 23.3% had some digestive system manifestations, 20.0% had circulatory system manifestations, 6.7% had hematologic manifestations, 6.7% had urinary system manifestations, 3.3% had arthritis manifestations, and 3.3% had central nervous system manifestations.

3.4 | Clinical characteristics, atopy, and specific allergen sensitizations in patients in the extrapulmonary and pulmonary groups

As shown in Table 4, 30 (20.0%) subjects were assigned to the extrapulmonary group, and the other 120 (80.0%) were assigned to the pulmonary group. Compared with the pulmonary group, the extrapulmonary group exhibited a higher prevalence of atopy (60.0% vs. 25.0%, respectively, $P = 0.000$), but the prevalence of allergen sensitization patterns did not differ between the groups (all $P > 0.05$, Table 4). Accordingly, the extrapulmonary group had a significantly higher total serum IgE level than the pulmonary group (176.5 [75.8-392.3] IU/mL vs. 89.5 [41.4-201.0] IU/mL, respectively, $P = 0.009$). However, the IL-17 levels were significantly lower in the extrapulmonary group than in the pulmonary group (436.5 ± 174.9 pg/mL vs. 535.1 ± 182.9 pg/mL, respectively, $P = 0.009$). There were no significant differences in age, gender, duration of hospitalization, fever, duration of fever, macrolide medicine uses for more than 7 days of illness, types of pneumonia, white blood cell counts, eosinophil counts, or CRP levels between the two groups ($P > 0.05$, Table 4).

TABLE 2 Comparison of respiratory severity between atopic and nonatopic children with MP pneumonia

	Atopy	Nonatopy		
	n = 48	n = 102	Test	*P*-value
Severity of diseases, n (%)			50.473	0.000
Severity	33 (68.8)	12 (11.8)		
Non-severity	15 (31.2)	90 (88.2)		
Pleural effusion, n (%)	6 (12.5)	4 (3.9)	2.605	0.107
Tachypnea[a]	12 (25.0)	4 (3.9)	15.219	0.000
Cyanosis	3 (6.3)	1 (1.0)	1.757	0.185
Oxygen treatment, n (%)	17 (35.4)	11 (10.8)	13.044	0.000
Steroid treatment, n (%)	21 (43.8)	27 (26.5)	4.479	0.034
Duration of steroid therapy (d)	5.4 ± 1.9	3.9 ± 1.2	3.363	0.002
Organ failure, n (%)	0 (0)	0 (0)		
Mechanical ventilation, n (%)	0 (0)	0 (0)		
Death, n (%)	0 (0)	0 (0)		

MP, *Mycoplasma pneumoniae*.
[a]Tachypnea: infants, respiratory rate > 70 breaths/min; older children, respiratory rate > 50 breaths/min.

4 | DISCUSSION

Mycoplasma pneumoniae is primarily an extracellular pathogen that requires tight cell contact for survival. It is able to penetrate the cell membrane of host cells and to invade the respiratory mucosa; moreover, it can lead to pronounced inflammatory responses and may also spread outside the respiratory system, to some extent. Thus, MP infection can result in extrarespiratory manifestations, as well as respiratory diseases.

Mycoplasma pneumoniae infection in children is a risk factor for developing allergic diseases and induces allergy.[14,15] Several studies have linked respiratory MP infection to asthma exacerbations, and there is some evidence that MP might elicit a T helper type 2 (Th2) immune response in the bronchial system.[16] In our study, the serum total IgE levels were higher in the atopic patients than in the nonatopic patients. These results support the previous finding that atopy is associated with an aberrant response to allergens through IgE production by antigen-specific Th2 cells and B cells.[17,18] In addition, we also found that the prevalences of asthma attack and a previous history of asthma were significantly higher in the atopic children than in the nonatopic children, which suggested that atopic children with MP pneumonia have a high risk of asthma attack.

TABLE 3 Extrapulmonary manifestation of MP pneumonia in children

Complications	n (%)
Skin manifestations	11 (36.7)
Digestive system	7 (23.3)
Circulatory system	6 (20.0)
Hematologic	2 (6.7)
Urinary system	2 (6.7)
Arthritis	1 (3.3)
Central nervous system	1 (3.3)

MP, *Mycoplasma pneumoniae*.

TABLE 4 Clinical characteristics, atopy, and specific allergen sensitization in patients with extrapulmonary and those with pulmonary

	Extrapulmonary	Pulmonary		
	n = 30	n = 120	Test	*P*-value
Demographics				
Age (y)	6.6 ± 2.7	6.6 ± 2.8	−0.015	0.988
Gender (M/F)	14/16	63/57	0.327	0.684
Fever > 38℃, n (%)	21 (70.0)	91 (75.8)	0.432	0.639
Duration of fever >10 d, n (%)	6 (20.0)	13 (10.8)	1.089	0.297
Macrolide medicine more than 7 d of sickness, n (%)	7 (23.3)	17 (14.2)	0.896	0.344
Duration of hospitalization (d)	9.2 ± 2.3	8.4 ± 2.1	1.869	0.064
Type of pneumonia, n (%)				
Bronchopneumonia	16 (53.3)	78 (65.0)	1.396	0.292
Lobar pneumonia	14 (46.7)	42 (35.0)		
Laboratory				
White blood cell (×/μL)	7581.0 ± 3667.3	6920.0 ± 3541.4	0.908	0.365
LogTEC (×/μL)	2.3 ± 0.3	2.2 ± 0.3	0.738	0.462
CRP (mg/L)	8.4 (2.8-30.3)	10.0 (2.2-23.3)	−0.268	0.791
IL-17 (pg/mL)	436.5 ± 174.9	535.1 ± 182.9	−2.661	0.009
Total IgE (IU/mL)	176.5 (75.8-392.3)	89.5 (41.4-201.0)	−2.589	0.009
Atopy, n (%)	18 (60.0)	30 (25.0)	13.511	0.000
Dermatophagoides farina	3 (10.0)	10 (8.3)	0.000	1.000
Dermatophagoides pteronyssinus	8 (26.7)	15 (12.5)	2.699	0.100
Cats dander	1 (3.3)	4 (3.3)	0.000	1.000
Dogs dander	4 (13.3)	5 (4.2)	2.135	0.144
Alternaria	3 (10.0)	2 (1.7)	2.909	0.088
Cockroach	2 (6.7)	2 (1.7)	2.312	0.179
Tree pollen mixture	4 (13.3)	5 (4.2)	2.135	0.144
Weed pollen mixture	4 (13.3)	4(3.3)	2.979	0.084

CRP, C-reactive protein; IL-17, interleukin-17; LogTEC, logarithmic transformation of total eosinophil count.

More importantly, more children in the atopic group than in the nonatopic group developed severe MP pneumonia and were likely to present with tachypnea, oxygen therapy use, and steroid therapy use. These findings indicated that the presence of atopy may be associated with severe MP pneumonia and with significantly greater difficulty in successful managing MP pneumonia. Atopy may have an adverse impact on disease severity; therefore, MP pneumonia patients with atopy are treated more aggressively with macrolide antibiotics and glucocorticoids.

In addition, we found that the rate of atopy was higher in the patients with extrapulmonary manifestations than in those without extrapulmonary manifestations. Interestingly, the serum total IgE levels were also higher in the extrapulmonary group than in the pulmonary group, which was consistent with the findings in the recent reports.[7,8] The increased IgE levels can be considered a marker of immune dysregulation.[19,20] These findings may partly explain the relationship between atopy and extrarespiratory manifestations and indicate that an individual with an atopic predisposition could have an additional stimulation driving IgE production during MP infection; as a consequence, this individual might develop some self-reactive IgEs that promote immune-mediated diseases and manifestations.

IL-17 is a key cytokine in the host defense against infections as well as in autoimmune diseases. In addition, it also plays a key role in the pathophysiology of atopic eczema/dermatitis syndrome.[21] In our study, the serum IL-17 levels were significantly lower in the atopic children than in the nonatopic children. Furthermore, we found that more atopic children developed severe MP pneumonia. This finding was in accordance with the results in recent reports, which showed

that a decreased IL-17 level is a valuable biomarker in severe MP pneumonia children.[22]

In addition, the serum IL-17 levels were also significantly lower in the extrapulmonary group than in the pulmonary group, which may indicate that the immunoregulatory function of IL-17 is insufficient in these children. These findings partly explain the recent report that more children in a high-MP-load group than those in a low-MP-load group presented with extrapulmonary manifestations and atopic conditions.[9] Pan et al[23] recently reported that the decrease in the peripheral basophil count in patients with systemic lupus erythematosus (SLE) might be due to the migration of these cells to the lymph nodes after their activation by autoreactive IgE. However, basophils can promote Th17 differentiation in SLE. Thus, a reduction in the IL-17 level in a murine model made the mice prone to developing an autoimmune disease. These findings may partly explain the occurrence of the reason that the patients with extrarespiratory manifestations had increased IgE and decreased IL-17 levels.

The present study had limitations. It studied a relatively small cohort. Furthermore, a multicenter, large-scale study is required to confirm our findings. However, to our knowledge, this is the first study investigating the roles of atopy in disease severity and extrapulmonary manifestations and elucidating disease pathogenesis.

In conclusion, atopy may be a risk factor for disease severity and extrapulmonary manifestations in children with MP pneumonia. Furthermore, it may be related to some potential and concomitant immune mechanisms, such as basophil-dependent autoreactive IgE and IL-17.

ACKNOWLEDGMENTS

The authors express their sincere gratitude to all participants and workers who contributed to this study. Funding support for this study was provided by the Tianjin Health Bureau Foundation of China (2014KZ049).

AUTHOR CONTRIBUTIONS

Zhihua Wang developed the original idea, designed the study, collected the data, wrote the article, and is the guarantor. Jian Sun contributed to the data analysis and participated in drafting the article. Yushui Wang participated in collecting the data and writing the article. Yan Liu participated in collecting the data and writing the article. All authors contributed toward data analysis, drafting and critically revising the article and agree to be accountable for all aspects of the work.

ETHICAL APPROVAL

This study was approved by the Research Ethics Committee of Tianjin Nankai Hospital (NKYY_YX_IRB_2018_029_01). Our study complies with the ethical standards required by this journal.

DATA ACCESSIBILITY

Please contact the author for data requests.

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How to cite this article: Wang Z, Sun J, Liu Y, Wang Y. Impact of atopy on the severity and extrapulmonary manifestations of childhood *Mycoplasma pneumoniae* pneumonia. *J Clin Lab Anal*. 2019;33:e22887. https://doi.org/10.1002/jcla.22887