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European Journal of Inflammation

Letter to the Editor

European Journal of Inflammation
Volume 16: 1–5
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DOI: 10.1177/2058739218772246
journals.sagepub.com/home/eji
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Clinical features of *Mycoplasma pneumoniae* infection in respiratory tract in children in middle south of China

Lili Zhou,[1] Wei Wang,[2] Xuyun Peng,[1] Bingfei Li,[1] Jing Li,[1] Jianping Liu[1] and Lin Yang[1]

Abstract

Mycoplasma pneumoniae (MP) is the smallest microorganisms which can survive independently in the world. It is a pathogen between the bacteria and the virus, mainly violates the respiratory system. Nasopharyngeal aspirates were collected from children with respiratory infection from April 2013 to November 2016 in a hospital in Jiangxi, China. A total of 4350 children were enrolled and nine viruses and eight bacteria, including *MP*, were tested by polymerase chain reaction (PCR) and culture. The total positivity rate of any viruses and bacteria was 73.6%; bacteria-positive detection rate was 34.5%; virus-positive detection rate was 49.1%; and mixed-positive detection rate was 45.4%. A total of 596 cases were identified as *MP*-positive, among which 274 cases were *MP*-positive only. *MP* was detected throughout the year and across all age groups. When compared with those of the respiratory syncytial virus (RSV)-positive only group, the *MP*-positive only group was consisted of older children and presented a higher percentage of fever, a longer duration of fever, and a lower percentage of wheezing. High load of *MP*-positive only group was detected mainly in preschool and school-aged children. Longer fever duration and severe cough symptoms were observed in the high load of *MP*-positive only group with high levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and D-dimer. The *MP*-positive only group with high load could be an etiological agent of severe respiratory tract infections.

Keywords

children, high load, *Mycoplasma pneumoniae*, respiratory tract infection, RT-PCR

Date received: 28 September 2017; accepted: 22 March 2018

Introduction

Mycoplasma pneumoniae (MP) is a common pathogen causing respiratory diseases in children. Long duration, serious symptoms, and severe cases can lead to atelectasis, pleural effusion, bronchitis obliterans, and so on in some patients.[1] *MP* can cause extrapulmonary manifestations in almost every organ, including the skin and the hematologic, cardiovascular, musculoskeletal, and nervous systems.[2] Treatment of *MP* infection includes macrolides and quinolones;[3] however, macrolide resistance rate is considerably high worldwide, particularly in China.[4] If the disease can be diagnosed accurately and quickly, selection of antibiotics can be more highly targeted, and

[1]Department of Respiratory Medicine, Women and Children's Hospital, Ganzhou, China
[2]Health School of Ganzhou, Ganzhou, China

Corresponding author:
Lili Zhou, Department of Respiratory Medicine, Women and Children's Hospital, Ganzhou 341000, Jiangxi, China.
Email: zhou1987117@126.com

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enhanced clinical effect can be achieved. *Mycoplasma pneumoniae pneumonia* (MPP) lacks specific clinical manifestations, and as such, its diagnosis relies on the determination of the etiology. Timely and effective laboratory diagnosis of *MP* infection is highly important to guide clinical treatment, preventing potential epidemics and complications. This study aimed to investigate the clinical characteristics of *MP*-positive only in children by real-time fluorescence quantitative polymerase chain reaction (RT-PCR) and to explore the significance of this method in the clinical diagnosis of *MP* infection.

Materials and methods

Study patients

Inclusion criteria were as follows: hospitalized children with respiratory tract infection in a respiratory ward were enrolled in this prospective study from April 2013 to November 2016 at Ganzhou Women and Children's Hospital in Jiangxi, China. Patients who presented with clinical signs and symptoms of pneumonia underwent chest radiography, and the pneumonia pattern was characterized based on the World Health Organization standardized interpretation of chest radiographs for the diagnosis of community-acquired pneumonia (CAP) in children.[5] The demographic data and clinical history were collected by interviewing their guardians.

Laboratory tests

Nasopharyngeal aspirates from patients were collected with a standardized technique using a disposable sterilized cotton swab. The specimens were maintained at 4°C for a maximum of 4 h and then transported to the inspection department of our hospital for further processing. The viral DNA and RNA were extracted from 200 μL aliquots of the nasopharyngeal aspirate samples by using the QIAamp MinElute Virus Spin Kit (Qiagen, Hilden, Germany). RNA was applied as the template for complementary DNA (cDNA) synthesis using the SuperScript III First-Strand Synthesis System (Invitrogen, Carlsbad, CA, USA). DNA and RNA extractions, as well as cDNA products, were used for subsequent testing of nine respiratory viruses:[6] *respiratory syncytial virus subgroup A* (*RSVA*); *respiratory syncytial virus subgroup B* (*RSVB*); *influenza virus A* (*IVA*); *influenza virus B* (*IVB*); *influenza virus C* (*IVC*); *human coronaviruses* (*CoV*); *metapneumovirus* (*MPV*); *parainfluenza virus* (*PIV*) *and adenovirus* (*AdV*). RT-PCR was employed to detect the *MP* load. Sputum culture was also conducted to detect bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*).[7] All of the children were tested for *MP* and respiratory syncytial virus (RSV) by RT-PCR.[8,9] Clinical characteristics of children with *MP* single infection were retrospectively analyzed.

Statistical analyses

The data were analyzed using SPSS version 17.0. Statistics for continuous variables are reported as mean ± standard deviation. Patient age may be associated with the levels of certain laboratory indices, including white blood cell count and C-reactive protein (CRP); thus, these quantitative data were transformed into categorical data (normal or abnormal). Statistical significance was assessed using the chi-square test or Fisher's exact test for categorical variables, as well as the t-test and analysis of variance (ANOVA) for continuous variables. A two-sided $P < 0.05$ was considered statistically significant.

Results

Demographic, clinical, and virological characteristics

A total of 4350 samples were tested by PCR from April 2013 to November 2016. The total positive rate of samples was 73.6%. The bacterial positive detection rate was 34.5%, and the virus-positive detection rate was 49.1%. The mixed-positive detection rate was 45.4%. *MP* was detected positive in 596 (13.7%) cases, among which only 274 (46.0%) were positive for MP only. The main pathogens co-infected with *MP* were *S. pneumoniae, H. influenzae, K. pneumonia*, and *influenza virus*. Among the samples, 114 were *RSV*-positive only and were used as the control group. Thus, 388 specimens were included in the statistics.

Among the 274 *MP*-positive only cases, the median age was 35.12 months (range: 1–156 months). A total of 81 (29.6%) children were aged<1 years, 92 (33.6%) were aged 1–3 years, 59 (21.5%) were

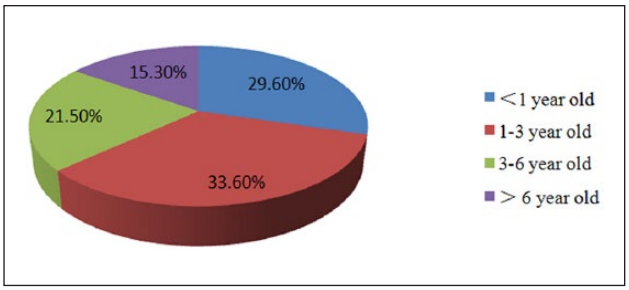


Figure 1. *Mycoplasma pneumonia* single-detection positive rate in different age groups.

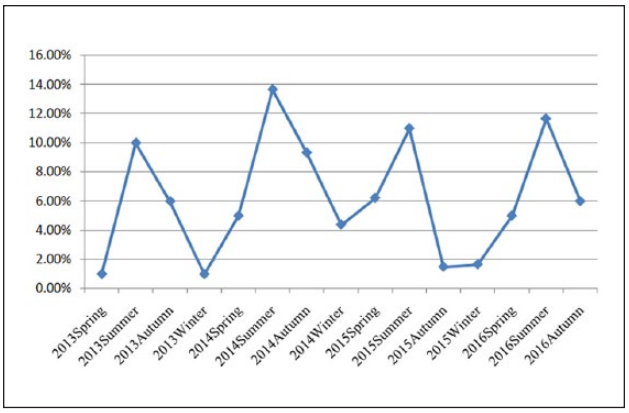


Figure 2. The detection rate of *MP* in each season.

aged 3–6 years, and 42 (15.3%) were aged >6 years. These data are presented in Figure 1.

The male-to-female sex ratio was 1.69:1. The main clinical diagnosis included bronchial pneumonia (181, 66.1%), bronchitis (55, 19.9%), and upper respiratory tract infection (31, 11.3%).

Characteristics of MP-positive only samples by RT-PCR

Significant seasonal differences were observed in the *MP*-positive only samples. These differences were detected throughout the year, with the highest detection rate obtained in summer and the low detection rate obtained in winter (see in Figure 2).

Comparison between the *MP*-positive only group and the *RSV*-positive only group with respect to the demographic factors, clinical characteristics, and laboratory examination is presented in Table 1. Children in the *MP*-positive only group were considerably older than the children in the *RSV*-positive only group (35.1 vs 7.2 months, $P<0.001$). In the *MP*-positive only group, the proportion of children with fever was larger (196 vs 47, $P<0.001$), the duration of fever was longer (6.64 vs 4.34 days, $P=0.028$), the maximum body temperature was higher (39.2°C vs 39.01°C, $P=0.036$), and the course of the disease was longer (16.12 vs 14.25 days, $P=0.018$), compared with those in the *RSV*-positive only group. However, the proportion of children with wheezing was smaller in the *MP*-positive only group than in the *RSV*-positive only group (63 vs 54, $P<0.001$).

Comparison between high-load group and low-load group in MP-positive only children

The 274 *MP*-positive only children were arbitrarily divided into two groups according to their bacterial loads: $>10^5$ copies for high-load group (n=63) and $<10^5$ copies for low-load group (n=211). Comparison of the two groups with respect to demographic factors, clinical characteristics, and laboratory examination is presented in Table 2. The high-load group mainly contained preschool and school-aged children: 15 (23.8%) were aged between 3–6 years and 21 (33.3%) were aged >6 years. The children in the high-load group were older than those in the low-load group (52.11 vs 30.12 months, $P<0.001$). In the high-load group, the proportion of children with cough was larger (100% vs 89.7%, $P=0.044$), the duration of fever (7.53 vs 6.32 days, $P=0.044$) was longer, and the course of the disease (18.14 vs 15.51 days, $P<0.001$) was longer, compared with the low-load group. The CRP (16.5 vs 10.36 mg/L, $P=0.048$), lactate dehydrogenase (LDH; 436.38 vs 223.11 IU/L, $P=0.000$), erythrocyte sedimentation rate (ESR; 56.7 vs 50.26 mm/h, $P=0.018$), and D-dimer (1.67 vs 0.65 mg/L, $P=0.000$) levels were higher in the high-load group than in the low-load group.

Discussion

This study suggested that the total *MP*-positive rate was 13.7% by RT-PCR. There were significant seasonal differences in *MP*-positive samples, which were detected in all ages throughout the year, with the highest detection rate in summer. The *MP*-positive only group was consisted of older children and presented a high percentage of fever, a long duration of fever, and a low percentage of wheezing. It was found that *MP* copy number has obvious correlation with disease severity.

Table 1. Comparison of the clinical features between MP-positive only group and RSV-positive only group.

	MP-positive only (n = 274)	RSV-positive only (n = 114)	*P*
Age (months)	35.12 ± 33.44	7.2 ± 6.95	<0.001
Sex (male)	174 (63.5%)	83 (72.8%)	0.078
Course of disease (days)	16.12 ± 9.82	14.25 ± 8.52	0.018
Fever	196 (71.5%)	47 (41.2%)	<0.001
The highest temperature (°C)	39.2 ± 0.69	39.01 ± 0.65	0.036
Duration of fever (days)	6.64 ± 6.01	4.34 ± 2.51	0.028
Cough	252 (91.9%)	110 (96.5%)	0.145
Wheezing	63 (23.0%)	54 (47.4%)	<0.001
Lung auscultation with wet rales	147 (53.8%)	63 (55.3%)	0.8
White blood cell ($10^9 L^{-1}$)	10.28 ± 5.09	11.39 ± 4.33	0.001
Neutrophil ratio (%)	49.52 ± 20.15	35.91 ± 16.6	<0.001
Lymphocyte ratio (%)	42.0 ± 19.4	54.22 ± 16.15	<0.001
Hemoglobin (g/L)	116.92 ± 12.31	117.78 ± 14.25	0.234
Platelets ($10^9 L^{-1}$)	368.57 ± 124.87	456.86 ± 141.09	<0.001
CRP (mg/L)	11.75 ± 18.51	10.1 ± 33.04	0.192
PCT (ng/mL)	0.17 ± 0.45	0.15 ± 0.39	0.236

MP: *Mycoplasma pneumoniae*; RSV: respiratory syncytial virus; CRP: C-reactive protein; PCT: procalcitonin.

Table 2. Comparison of the clinical features between high load and low load with MP single-detection positive.

	High load (n = 63)	Low load (n = 211)	*P*
Age (months)	52.11 ± 39.26	30.12 ± 29.79	<0.001
Sex (male)	32 (50.8%)	142 (67.3%)	0.017
Course of disease (days)	18.14 ± 9.85	15.51 ± 9.76	<0.001
Fever	51 (81.0%)	145 (68.7%)	0.059
The highest temperature (°C)	39.24 ± 0.75	39.18 ± 0.67	0.577
Duration of fever (days)	7.53 ± 7.02	6.32 ± 5.61	0.044
Cough	63 (100%)	189 (89.7%)	0.044
Wheezing	10 (15.9%)	53 (25.1%)	0.126
White blood cell ($10^9 L^{-1}$)	9.49 ± 5.46	10.5 ± 4.98	0.095
Neutrophil ratio (%)	53.88 ± 15.93	48.32 ± 21.04	0.093
Lymphocyte ratio (%)	38.34 ± 16.14	43.01 ± 20.15	0.172
Hemoglobin (g/L)	117.68 ± 12.75	116.71 ± 12.56	0.575
Platelets ($10^9 L^{-1}$)	346.9 ± 122.3	374.05 ± 125.34	0.196
CRP (mg/L)	16.5 ± 24.84	10.36 ± 16.02	0.048
PCT (ng/mL)	0.17 ± 0.32	0.16 ± 0.45	0.505
LDH (IU/L)	436.38 ± 54.21	223.11 ± 33.81	0.000
ESR (mm/h)	56.7 ± 7.1	50.26 ± 6.32	0.018
D-Dimer (mg/L)	1.67 ± 0.25	0.65 ± 0.09	0.000

MP: *Mycoplasma pneumoniae*; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

Approximately 3%–10% of children with *MP* respiratory infection develop CAP, and <5% of CAP cases are severe enough to require hospitalization. In one study, *MP* could be detected by PCR in 178 (8%) of 2179 cases of CAP.[10] The clinical characteristics of *MP*-positive only children detected by RT-PCR mainly consist of the following: large proportion of older children, high rate of occurrence of fever, long duration of fever, and low wheezing ratio. The high load of *MP*-positive only group consisted mainly of preschool and school-aged children. The proportion of children in the high-MP load group suffered from a longer duration of fever and more significant cough, which confirmed to the clinical features of *MP* infection.[11] Nilsson et al.[12] also found that the load of *MP* was proportional to the severity of illness. Studies have shown that the higher the *MP* load in the alveolar lavage of the children with MPP, the more severe the clinical symptoms. The *MP* load

exhibits high correlation with the severity of the disease. The higher the *MP* load, the higher the occurrence rate of severe pneumonia and lobar pneumonia.[13] The D-dimer concentration in the high-load group was significantly higher than that in the low-load group, which helped evaluate the progress of the disease. This study found that determining *MP* load by RT-PCR provided an early assessment for the severity of *MP* pneumonia. RT-PCR is worthy to be widely spread. It requires further research.

Acknowledgements

We thank all the families for their enrollment in this study. We also thank the staff in the Department of Respiratory Medicine.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study was approved by the Ethics and Research Council of Women and Children's Hospital of Ganzhou, and signed consent was obtained from each child's parents or foster parents.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

L.Z. contributed to the concept and design of the study, analyzed and interpreted the data, and assisted in the critical writing. W.W., X.P., and L.L. helped to perform the MP and RSV detection procedures. J.L. and Y.L. contributed to the collection of clinical information. B.L. contributed to the concept and design of the study. All authors read and approved the final manuscript.

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