The Incidence and Risk Factors of Extrapulmonary Manifestations in Mycoplasma Pneumoniae Pneumonia

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Abstract

Background: *Mycoplasma pneumoniae* pneumonia (MP) is a major cause of community acquired pneumonia (CAP) in children and it is known to be associated with extrapulmonary manifestations (EPM). The incidence and risk factors of EPM in children are not known.

Methods: This is a retrospective study involving 65,243 pediatric CAP patients between 2010 and 2015 at 23 nationwide hospitals was conducted in South Korea. The medical records were reviewed to collect the information regarding the clinical characteristics, radiological results, and laboratory findings. In total, 9,190 children with MP were identified and included in the analysis. Logistic regression with multivariable analysis was performed to evaluate the risk factors associated with EPM in MP.

Results: The mean age of the enrolled patients with MP was 64.3 ± 39.8 months, and the proportion of male patients was 49.5%. The incidence of EPM was 23.9% and included elevation of liver enzymes (18.1%), mucocutaneous manifestations (4.4%), proteinuria (4.1%), cardiovascular and neurologic manifestation (0.4%), hematologic manifestation (0.2%) and arthritis (0.2%). Statistical analysis showed that mucocutaneous manifestations were significantly increased with elevated alanine aminotransferase (adjusted odds ratio [aOR] 3.623, 95% confidence intervals [CI] 1.933-6.790) and atopic sensitization (aOR 2.973, 95% CI 1.615-5.475) and decreased with respiratory virus co-infection (aOR 0.273, 95% CI 0.084-0.887). Elevated liver enzymes was significantly associated with the elevation of lactate dehydrogenase (aOR 3.055, 95% CI 2.257-4.137) and presence of pleural effusion (aOR 2.635, 95% CI 1.767-3.930) and proteinuria with respiratory virus co-infection (aOR 2.245, 95% CI 1.113-4.527).

Conclusions: About 24% of pediatric MP patients were identified with various EPM. Since risk factors associated with each EPM was different, it is necessary to evaluate the various clinical aspects and findings of MP to predict and prepare for the occurrence of EPM.

Introduction

Mycoplasma pneumoniae is one of the most common pathogens responsible for community acquired pneumonia (CAP) in children, which is characterized by fever, cough, and sputum and considerable portion of children need hospitalization [1, 2]. *Mycoplasma pneumoniae* pneumonia (MP) epidemic occurs in Korea about every 3 to 4 years [3], and could lead to increased burden in pediatric community. The characteristics of MP are various from self-limiting to having long-term sequelae such as bronchiolitis obliterans and bronchiectasis [4]. In addition, macrolide-resistant MP (MRMP) is emerging issue these days [5–7].

Besides respiratory symptoms, MP pathogenesis can also involve extrapulmonary manifestations (EPM) that affect almost all the body organs and are associated with mucositis, Stevens-Johnson syndrome (SJS), rash, tendinitis, and central nerve system infection. Mycoplasma infection can lead to several EPM such as proteinuria, acute hepatitis, myocarditis, Kawasaki disease, peripheral neuropathy, Guillain-Barré syndrome and hemophagocytic syndrome [8–10]. The incidence of EPM and the associated risk factors

have not been extensively studied. Furthermore, although MP is a common cause for CAP, the mechanism of MP-driven periodic epidemics and etiology of various clinical characteristics, including EPM, are not yet understood leading to difficult treatment.

Macrolides are the first-choice antibiotic agents for the treatment of MP in children. However, MRMP are increasing abruptly [5–7] resulting in clinical deterioration despite treatment [11–14]. MRMP could be treated with tetracycline and quinolones; however, their use in pediatric patients is limited due to safety concerns, such as permanent tooth discoloration by tetracycline and side effects involving muscles, tendons or joints by quinolones. It has also been reported that MRMP could be a risk factor for the development of EPM [11]; therefore, careful observation is necessary in MRMP patients.

In this study, we aimed to study clinical aspects of pediatric MP patients and to evaluate the incidence of EPM and associated risk factors.

Methods

Study population

This study was conducted based on the data collected from 23 medical centers on pediatric CAP patients hospitalized between January 1, 2010 and December 31, 2015. The data were collected in cooperation with secondary and tertiary medical centers under the 'Pneumonia and Respiratory Diseases study group' of the Korean Academy of Pediatric Allergy and Respiratory Disease [3]. Data from a total of 65,243 pediatric CAP patients under the age of 18 years were collected by a retrospective chart review. Of these, patients of 9,190, diagnosed with MP, were included in this analysis.

To identify differences in incidence of EPM according to age, two age groups were considered; (1) preschool children (< 60 months old) and (2) schoolchildren ($\geq$ 60 months old).

Clinical characteristics, including respiratory symptoms with or without intensive treatment, underlying diseases, prescribed drugs, and laboratory and radiological findings were collected from a retrospective chart review of medical records.

The study protocol was approved by the Institutional Review Boards of all participating medical centers. This study was approved by the Institutional Review Board and Ethics Committee of Soonchunhyang University Seoul Hospital (SCHUH201-309013001).

Definition of *Mycoplasma pneumoniae* pneumonia

Pneumonia was diagnosed by pediatricians based on both physical examinations and radiological assessments [1]. MP was considered when: (1) a 4-fold or greater increase in IgM and/or IgG antibody titers between acute and convalescent stages was observed and/or (2) polymerase chain reaction (PCR) showed positive results for mycoplasma in nasopharyngeal aspiration or sputum samples [5, 15].

The response of patients with MP to macrolide treatment was divided into three categories based on the fever duration in each pneumonia episode after the initiation of macrolide treatment, regardless of the macrolide sensitivity test results. We defined clinical macrolide-sensitive MP (MSMP), macrolide-refractory MP (MRMP), and macrolide-less effective MP (MLMP) as fever for ≤ 3 days after the macrolide treatment, > 7 days, and >3 days but ≤ 7 days, respectively [3].

Extrapulmonary manifestations of Mycoplasma pneumoniae pneumonia

EPM were classified into seven categories as elevation of liver enzyme, mucocutaneous manifestations (rash, urticaria, SJS, erythema multiforme, and mucositis), proteinuria, cardiovascular (myocarditis and Kawasaki disease), neurologic (encephalitis, meningitis, peripheral neuropathy, transverse myelitis and Guillain-Barré syndrome) and hematologic manifestations (hemolytic anemia, thrombocytopenia, hemophagocytic syndrome and disseminated intravascular coagulation) and arthritis.

Laboratory and radiologic studies

Real-time PCR (RT-PCR) analyses were performed to identify the causative respiratory viruses; adenovirus, human rhinovirus, influenza virus, parainfluenza virus, human metapneumovirus, respiratory syncytial virus, bocavirus, and human coronavirus were identified.

The laboratory results were including complete blood count (CBC) with differential counts, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH).

Chest X-ray findings were classified as bronchopneumonia and lobar pneumonia with or without pleural effusion and atelectasis in the worst condition.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation and frequency (percentage) for categorical variables. Differences in baseline characteristics between groups were explored using independent two sample *t*-test and chi-square test (or Fisher's exact test) where appropriate.

To identify the independent risk factors for EPM, a multivariable logistic regression model was performed using a enter method that included variables with a probability value < 0.05 in the univariable analysis. Odd ratios (OR) and their 95% confidence intervals (CI) were also calculated.

A two-tailed *P*-value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Result

Characteristics of the study participants

The clinical characteristics of the pediatric patients of this study are presented in Table 1. The mean age of the 9,190 enrolled children with MP was 64.3 months. EPM were observed in older children ($P < 0.001$), however there was no difference in EPM occurrence between schoolchildren and preschool children ($P = 0.141$). The portion of male and female patients was similar (49.5% vs. 50.5%), although EPM occurred more frequently in male patients (51.9% vs 48.1%, $P = 0.010$).

Table 1
Clinical characteristics of the study participants

Variables	Total (n=9190)	Without EPM (n=6998)	With EPM (n=2192)	P value
Age (month)	64.3 ± 39.8	64.0 ± 39.7	70.9 ± 41.8	<0.001
< 60 months	4802 (52.3)	3627 (51.8)	1175 (53.6)	0.141
≥ 60 months	4387 (47.7)	3371 (48.2)	1016 (46.4)	
Sex				
Female	4643 (50.5)	3588 (51.3)	1055 (48.1)	0.010
Male	4547 (49.5)	3410 (48.7)	1137 (51.9)	
Groups depending on the response to macrolide treatment				
MSMP	7107 (77.3)	5649 (80.7)	1458 (66.5)	<0.001
MLMP	1613 (17.6)	1093 (15.6)	520 (23.7)	
MRMP	470 (5.1)	256 (3.7)	214 (9.8)	
Cyanosis	201 (2.3)	95 (1.5)	106 (5.0)	<0.001
Dyspnea	1241 (14.2)	855 (13.0)	386 (18.1)	<0.001
Oxygen treatment	409 (4.5)	248 (3.5)	161 (7.3)	<0.001
Ventilator treatment	16 (0.2)	4 (0.1)	12 (0.5)	<0.001
Any respiratory virus co-infection	1728 (18.8)	1245 (17.8)	483 (22.0)	<0.001
Past history / Underlying diseases				
Asthma	627 (7.2)	516 (7.9)	111 (5.2)	<0.001

Values are presented as a mean ± standard deviation or number (%)

EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia; ICU Intensive care unit

Variables	Total (n=9190)	Without EPM (n=6998)	With EPM (n=2192)	<i>P</i> - value
Atopic sensitization	552 (7.4)	438 (7.6)	114 (6.9)	0.326
Values are presented as a mean ± standard deviation or number (%)				
EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia; ICU Intensive care unit				

The proportion of MP depending on the patient responses to macrolide treatment was MSMP 7,107 (77.3%), MLMP 1,613 (17.6%), and MRMP 470 (5.1%). EPM were more common in children with MRMP than that with MSMP ($P < 0.001$). Children with respiratory difficulty, such as cyanosis and dyspnea, were more prone to develop EPM ($P < 0.001$) and therefore oxygen therapy and ventilator care were more accompanied in children with EPM ($P < 0.001$). Children with asthma history showed less EPM ($P < 0.001$), however, atopic sensitization was not associated with EPM ($P = 0.326$).

In addition to the clinical characteristics, laboratory and radiological findings were significantly different between children with and without EPM (Table 2). Liver enzymes and LDH were higher in children with EPM ($P < 0.001$, respectively), but CRP levels and ESR were not statistically different ($P = 0.111$ and $P = 0.958$, respectively). EPM were developed more in children with lobar pneumonia and pleural effusion ($P < 0.001$, respectively).

Table 2
Difference in laboratory and radiological findings depending on the presence of extrapulmonary manifestations

Variables	Without EPM (n=6998)	With EPM (n=2192)	P-value
Laboratory findings			
WBC (/mm ³)	9574 ± 4755	9194 ± 4747	0.119
AST (U/L)	42 ± 117	67 ± 141	<0.001
ALT (U/L)	26 ± 114	53 ± 111	<0.001
LDH (U/L)	517 ± 350	779 ± 614	<0.001
CRP (mg/dL)	7.7 ± 19.0	6.5 ± 14.2	0.111
ESR (mm/hr)	34 ± 23	34 ± 23	0.958
Radiological findings			
Lobar pneumonia	2558 (39.3)	972 (46.8)	<0.001
Pleural effusion	367 (5.6)	317 (15.6)	<0.001
Chest tube insertion	20 (0.3)	69 (3.1)	<0.001
Values are presented as a mean ± standard deviation or number (%).			
EPM extrapulmonary manifestations; WBC white blood cell; AST aspartate aminotransferase; ALT alanine aminotransferase; LDH lactate dehydrogenase; CRP C-reactive protein; ESR erythrocyte sedimentation rate.			

Incidence of extrapulmonary manifestations

The incidence of EPM in children with MP was 23.9% (Fig. 1). Elevation of liver enzyme was the most common EPM (18.1%). Among other EPM, mucocutaneous manifestation occurred in 4.4% of patients, and the skin rash was the most common (4.2%). Proteinuria (4.1%), cardiovascular manifestation (0.4%), neurologic manifestation (0.4%), hematologic manifestation (0.2%) and arthritis (0.2%) were the other EPM observed.

Risk factors associated with mucocutaneous manifestations

The univariable logistic regression model showed that the main parameters associated with mucocutaneous manifestation include schoolchildren, male patients, MRMP and MLMP, elevated ALT and LDH levels, respiratory virus co-infection, pleural effusion, and atopic sensitization (Table 3). Schoolchildren and male patients in comparison to preschool children (OR 1.474, 95% CI 1.204-1.803)

and female patients (OR 1.314, 95% CI 1.074-1.606) were more likely to develop mucocutaneous manifestations, respectively. According to the response to macrolide treatment, mucocutaneous manifestation was significantly higher in the MLMP and MRMP group than in the MSMP group (OR 1.867, 95% CI 1.473-2.367; OR 3.440, 95% CI 2.511-4.714, respectively). Laboratory findings showed that the elevated ALT and LDH levels were associated with increased incidence of mucocutaneous manifestation (OR 3.959, 95% CI 3.100-5.054; OR 2.251, 95% CI 1.641-3.088, respectively). Respiratory virus co-infection was negatively associated with mucocutaneous manifestation (OR 0.719, 95% CI 0.541-0.954), whereas pleural effusion was positively associated with mucocutaneous manifestation (OR 2.904, 95% CI 2.180-3.868). Furthermore, children with atopic sensitization were significantly associated with the occurrence of mucocutaneous manifestation (OR 1.954, 95% CI 1.361-2.806).

Table 3
Risk factors associated with mucocutaneous manifestations

Variables	Without EPM (n=8788)	With EPM (n=402)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Age groups				
< 60 months	4629 (52.7)	173 (43.0)	1.000	1.000
≥ 60 months	4158 (47.3)	229 (57.0)	1.474 (1.204-1.803)	0.625 (0.370-1.056)
Sex (male)	4322 (49.2)	225 (56.0)	1.314 (1.074-1.606)	1.154 (0.693-1.921)
Response to macrolide treatment				
MSMP	6859 (78.0)	248 (61.7)	1.000	1.000
MLMP	1511 (17.2)	105 (25.4)	1.867 (1.473-2.367)	0.438 (0.188-1.020)
MRMP	418 (4.8)	52 (12.9)	3.440 (2.511-4.714)	0.574 (0.244-1.352)
ALT (> 40 U/L)	626 (7.6)	96 (24.6)	3.959 (3.100-5.054)	3.623 (1.933-6.790)
LDH (> 479 U/L)*	1635 (48.9)	127 (68.3)	2.251 (1.641-3.088)	1.265 (0.727-2.202)
ESR (> 10 mm/hr)	4945 (86.0)	245 (87.8)	1.170 (0.811-1.688)	0.900 (0.463-1.750)
Respiratory virus co-infection	1670 (19.0)	58 (14.4)	0.719 (0.541-0.954)	0.273 (0.084-0.887)
Dyspnea	175 (2.1)	26 (7.3)	1.208 (0.909-1.604)	0.754 (0.328-1.732)
Pleural effusion	621 (7.6)	63 (19.2)	2.904 (2.180-3.868)	1.505 (0.709-3.193)

Values are presented as number (%) and significant results are represented in bold.

*median

EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia.

Variables	Without EPM (n=8788)	With EPM (n=402)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Atopic sensitization	516 (7.2)	36 (13.2)	1.954 (1.361-2.806)	2.973 (1.615-5.475)
Values are presented as number (%) and significant results are represented in bold.				
*median				
EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia.				

To assess the relationships between more than one predictor and the outcome, the multivariable logistic regression was also evaluated. The elevated ALT levels and atopic sensitization were found to be positively associated with mucocutaneous manifestation (aOR 3.623, 95% CI 1.933-6.790; aOR 2.973, 95% CI 1.615-5.475), whereas respiratory virus co-infection was negatively associated (aOR 0.273, 95% CI 0.084-0.887).

Risk factors associated with the elevation of liver enzymes

Table 4 shows the result of the univariable and multivariable analysis between elevated liver enzymes and various risk factors. The univariable logistic regression model showed that the schoolchildren were less likely to develop elevated liver enzymes (OR 0.538, 95% CI 0.462-0.625), while male patients was found to be associated (OR 1.125, 95% CI 1.012-1.251). Elevation of liver enzymes was significantly higher in the MLMP and MRMP group compared to MSMP group (OR 2.021, 95% CI 1.777-2.298; OR 3.230, 95% CI 2.648-3.941, respectively). Elevated LDH levels (OR 4.320, 95% CI 3.547-5.261), respiratory virus co-infection (OR 1.367, 95% CI 1.202-1.554), and dyspnea (OR 1.523, 95% CI 1.323-1.755) increased the risk of elevation of liver enzymes. Similarly, pleural effusion increased the risk of elevation of liver enzymes (OR 3.312, 95% CI 2.810-3.904), however, atopic sensitization was not significantly associated (OR 0.827, 95% CI 0.647-1.057).

Table 4
Risk factors associated with elevated liver enzymes

Variables	Without EPM (n=7525)	With EPM (n=1665)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Age groups				
< 60 months	925 (12.3)	352 (21.1)	1.000	1.000
≥ 60 months	2927 (38.9)	599 (36.0)	0.538 (0.462-0.625)	0.869 (0.660-1.143)
Sex (male)	3683 (48.9)	864 (51.9)	1.125 (1.012-1.251)	1.233 (0.994-1.609)
Response to macrolide treatment				
MSMP	6038 (80.2)	1069 (64.2)	1.000	1.000
MLMP	1188 (15.8)	425 (25.5)	2.021 (1.777-2.298)	0.862 (0.504-1.473)
MRMP	299 (4.0)	171 (10.3)	3.230 (2.648-3.941)	1.511 (0.879-2.600)
LDH (> 479 U/L)*	1261 (43.8)	501 (77.1)	4.320 (3.547-5.261)	3.055 (2.257-4.137)
ESR (> 10 mm/hr)	4137 (86.2)	1053 (85.6)	0.949 (0.793-1.135)	0.699 (0.488-1.000)
Respiratory virus co-infection	1346 (17.9)	382 (22.9)	1.367 (1.202-1.554)	1.176 (0.801-1.725)
Dyspnea	931 (13.2)	310 (18.8)	1.523 (1.323-1.755)	1.054 (0.709-1.566)
Pleural effusion	413 (5.9)	271 (17.3)	3.312 (2.810-3.904)	2.635 (1.767-3.930)
Atopic sensitization	472 (7.6)	80 (6.4)	0.827 (0.647-1.057)	1.317 (0.881-1.969)
Values are presented as number (%) and significant results are represented in bold.				
*median				
EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia.				

In multivariable analysis, elevated LDH levels and pleural effusion were significantly associated with elevation of liver enzymes (aOR 3.055, 95% CI 2.257-4.137; aOR 2.635, 95% CI 1.767-3.930, respectively).

Risk factors associated with proteinuria and other manifestations

The result of the univariable and multivariable analysis between proteinuria and various risk factors are shown in Table 5. The univariable logistic regression model showed more tendency of schoolchildren and male patients to develop proteinuria (OR 1.785, 95% CI 1.444-2.206; OR 1.235, 95% CI 1.004-1.519). Proteinuria was significantly higher with MLMP and MRMP group compared to MSMP group (OR 1.952, 95% CI 1.530-2.489; OR 3.592, 95% CI 2.604-4.954, respectively). Elevated ALT and LDH levels were also positively associated with proteinuria (OR 1.995, 95% CI 1.478-2.692; OR 2.269, 95% CI 1.608-3.204, respectively). Respiratory virus co-infection, dyspnea, and pleural effusion increased the risk of proteinuria (OR 1.306, 95% CI 1.160-1.470; OR 1.679, 95% CI 1.301-2.166; OR 2.746, 95% CI 2.060-3.660, respectively), whereas atopic sensitization was not significantly associated with proteinuria.

Table 5
Risk factors associated with proteinuria

Variables	Without EPM (n=8814)	With EPM (n=376)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Age groups				
< 60 months	4657 (52.8)	145 (38.6)	1.000	1.000
≥ 60 months	4156 (47.2)	231 (61.4)	1.785 (1.444-2.206)	1.488 (0.818-2.715)
Sex (male)	4342 (49.3)	205 (54.5)	1.235 (1.004-1.519)	1.389 (0.772-2.499)
Response to macrolide treatment				
MSMP	6879 (78.0)	228 (60.6)	1.000	1.000
MLMP	1515 (17.2)	98 (26.1)	1.952 (1.530-2.489)	0.689 (0.257-1.850)
MRMP	420 (4.8)	50 (13.3)	3.592 (2.604-4.954)	0.713 (0.259-1.966)
ALT (> 40 U/L)	668 (8.1)	54 (15.0)	1.995 (1.478-2.692)	1.981 (0.896-4.379)
LDH (> 479 U/L)*	1655 (49.0)	107 (68.6)	2.269 (1.608-3.204)	1.715 (0.896-3.281)
ESR (> 10 mm/hr)	4942 (85.9)	248 (89.9)	1.450 (0.974-2.158)	0.932 (0.420-2.067)
Respiratory virus co-infection	1628 (18.5)	100 (26.6)	1.306 (1.160-1.470)	2.245 (1.113-4.527)
Dyspnea	1161 (13.9)	80 (21.3)	1.679 (1.301-2.166)	1.374 (0.615-3.068)
Pleural effusion	622 (7.6)	62 (18.4)	2.746 (2.060-3.660)	1.868 (0.825-4.231)

Values are presented as number (%) and significant results are represented in bold.

*median

EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia

Variables	Without EPM (n=8814)	With EPM (n=376)	Univariable analysis OR (95% CI)	Multivariable analysis aOR (95% CI)
Atopic sensitization	537 (7.5)	15 (5.3)	0.686 (0.405-1.162)	0.749 (0.288-1.947)
Values are presented as number (%) and significant results are represented in bold.				
*median				
EPM extrapulmonary manifestations; MSMP macrolide-sensitive mycoplasma pneumonia; MLMP macrolide-less effective mycoplasma pneumonia; MRMP macrolide-resistant mycoplasma pneumonia				

Respiratory virus co-infection was the only factor that was significantly associated with proteinuria in multivariable logistic regression analysis (aOR 2.245, 95% CI 1.113-4.527).

Rare complications, such as cardiovascular, neurologic, and hematologic manifestations, and arthritis, did not show any association with the clinical, laboratory and radiological factors in the multivariable analysis (data not shown).

Discussion

MP is the common cause of CAP in children globally and is frequently associated with a wide range of EPM with or without respiratory symptoms [8]. In this study, the incidence of EPM in children with MP was 23.9%. Elevation of liver enzymes (18.1%) was the most frequently occurring EPM, followed by mucocutaneous manifestations (4.4%), proteinuria (4.1%), cardiovascular (0.4%), neurologic (0.4%), and hematologic manifestations (0.2%) and arthritis (0.2%). The factors associated with each EPM was different. Mucocutaneous manifestation was associated with elevated ALT and atopic sensitization, elevation of liver enzymes occurred more frequently with higher LDH levels and pleural effusion, and proteinuria was developed more with respiratory virus co-infection.

Mycoplasma pneumoniae is known to cause various EPM that affect several organs of the human body [8], although the exact mechanisms are not yet known. Possibly, it includes either the direct effect of mycoplasma pathogen itself or the indirect effect of the bacterium, such as autoimmunity or formation of immune complexes, and the last, vascular occlusion either directly or indirectly by mycoplasma [8, 16, 17]. Since EPM are distinguishable from other bacterial or viral pneumonia, they are always associated with mycoplasma. However, the incidence of EPM during mycoplasma infection are mostly reported in case reports [9, 10]. Therefore, it is important to investigate the incidence of EPM during mycoplasma infection through more studies. This study was aimed to evaluate the incidence of EPM associated with mycoplasma infection (23.9% of patients showed EPM). Previously, a report from China on 150 pediatric MP patients showed 20% incidence. Skin manifestation was the most frequent (36.7%) followed by the digestive system (23.3%) [16]. In the current study, they suggested that atopy may be a risk factor for the

EPM [16] and we have found the similar feature that atopic sensitization was significantly associated with mucocutaneous manifestation.

In this study, age and gender of the patients were the factors that may be associated with the development of EPM in MP. Many reports have confirmed that EPM owing to MP frequently occur in children [17]. A report showed that the incidence of EPM in adult was only 2.2% [18]. However, even among children, the incidence of EPM may be different and schoolchildren are more prone to occur EPM than preschool children are. In addition, increasing MRMP is an emerging issue and a previous study in China has shown that EPM are risk factors for refractory *Mycoplasma pneumonia* and macrolide resistance [11, 19]. EPM rates were significantly related to the extent of macrolide resistance, with the MRMP population is prone to have a higher risk of all complications. In our study, MRMP was also associated with the increased development of each EPM in univariable analysis. Higher levels of LDH have been reported to be related to MRMP [20] and could be another risk factor for EPM. Clinically and radiologically severe patients, such as those with pleural effusion, the requirement of oxygen supply or ventilator use, moderate to severe dyspnea and the need for ICU care, were at risk of developing EPM. Therefore, severe and macrolide non-responsive patients should be evaluated and considered for concomitant EPM in MP.

According to the findings of this study, each EPM is associated with different factors and requires further investigation to understand the mechanism that causes a particular EPM in MP. Mucocutaneous manifestations are more prominent in children with higher ALT levels and a history of atopic sensitization, but less frequently when respiratory viruses are co-infected. Abnormal liver function was associated with higher levels of LDH and pleural effusion, whereas proteinuria developed more in children with respiratory virus co-infection.

The strength of this study is that it was a multicenter study (n=23) with a large number of study participants (n=9,190). Previous studies were limited due to the involvement of less number of hospitals (one or two) and, hence could provide less patient data. Additionally, pediatric pulmonary specialists, participating in the Pneumonia and Respiratory Disease Study Group of Korean Academy of Pediatric Allergy and Respiratory Disease, have joined this study to evaluate and treat MP. However, this study was a retrospective study with chart review, and some missing data that may cause bias, suggesting the need for further prospective studies. Since the data collected in this study were from hospitalized in tertiary hospitals, more severe patients could have been analyzed.

In conclusion, we found that 23.9% of children with pediatric MP patients had EPM in Korea. Each EPM is associated with different factors. Mucocutaneous manifestations were increased with elevated ALT, and atopic sensitization and elevation of liver enzymes were associated with elevated LDH and pleural effusion. Respiratory virus co-infection is a risk factor for proteinuria. Further studies are needed to reveal the risk factors and pathophysiology of EPM of mycoplasma infection to prevent and effectively treat MP.

Abbreviations

MP, *Mycoplasma pneumoniae* pneumonia; CAP, community acquired pneumonia; EPM, extrapulmonary manifestations; MRMP, macrolide-resistant and/or macrolide-refractory mycoplasma pneumonia; MLMP, macrolide-less effective mycoplasma pneumonia; MSMP, macrolide-sensitive mycoplasma pneumonia; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Declarations

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Authors' contributions

Conceived and designed the study, recruited the necessary data: YKP, YNP, JEM, MYS, EL, CHK, JSL, TJL, BSK, HYK, SSJ, YSK, SYK, CRP, JHS, JYS, ISS, MSS, DJS, YMA, HLO, JHY, KSL, GCJ, YYJ, HLC, EHC, SMC, YJC, MYH, JTK, CKK and HBK.

Contributed to interpreting and analyzing the data: YKP, HBK, YNP and MYS.

Contributed to the writing of the manuscript: YKP, HBK, YNP and MYS.

All authors contributed to manuscript revisions. All authors read and approved the final manuscript.

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Availability of data and materials

The data used were collected through the routine surveillance systemic of Pneumonia & Respiratory Disease Study Group of Korean Academy of Pediatric Allergy and Respiratory Disease. Data are available from the authors upon reasonable request and with permission of the Pneumonia & Respiratory Disease Study Group of the Korean Academy of Pediatric Allergy and Respiratory Disease.

Ethics approval and consent to participate

With no personal information in each participant, the informed consent was waived because this was a retrospective medical record review research.

This study was approved by the Institutional Review Board and Ethics Committee of each participating hospital and Soonchunhyang University Seoul Hospital (SCHUH201-309013001).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

Figure 1

Incidence of extrapulmonary manifestations