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Increased risk of refractory *Mycoplasma pneumoniae* pneumonia in children with atopic sensitization and asthma

Jeong Eun Shin, MD, Bo Ram Cheon, MD, Jae Won Shim, MD, PhD, Deok Soo Kim, MD, PhD, Hae Lim Jung, MD, PhD, Moon Soo Park, MD, PhD, Jung Yeon Shim, MD, PhD
Department of Pediatrics, Kangbuk Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: A nationwide outbreak of *Mycoplasma pneumoniae* pneumonia (MP) refractory to macrolide antibiotics occurred in Korea during 2011. Steroid therapy has been reported to be both efficacious and well tolerated in pediatric patients with refractory MP. We compared clinical features and laboratory characteristics between children with refractory MP requiring steroid treatment and those with macrolide-responsive MP and evaluated the risk factors associated with refractory MP.
Methods: We investigated 203 children who were admitted to our institution with MP from June to November 2011. Refractory MP was defined by persistent fever over 38.3℃ with progressive pulmonary consolidation or pleural effusion despite administration of appropriate macrolide antibiotics for 5 days or longer after admission. Steroid therapy was initiated on the fifth day after admission for refractory cases.
Results: There were 26 patients with refractory MP requiring steroid therapy. The mean duration of steroid therapy was 5.4 days and most of the patients were afebrile within 24 hours after initiation of steroid therapy. The prevalence of refractory MP was higher in patients with pleural effusion, lobar pneumonia affecting more than 2 lobes, higher levels of serum lactate dehydrogenase, increased oxygen requirements, and longer duration of hospitalization. Atopic sensitization and history of asthma were also associated with refractory MP after adjusting for age and gender.
Conclusion: Children with refractory MP had more severe pneumonia. Atopic sensitization and history of asthma may be risk factors for refractory MP requiring steroid therapy in Korean children.

Key words: Asthma, Atopy, Child, Pneumonia, Mycoplasma

Corresponding author: Jung Yeon Shim, MD, PhD
Division of Pediatric Allergy & Pulmonology, Department of Pediatrics, Kangbuk Samsung Medical Center, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 110-746, Korea
Tel: +82-2-2001-2484
Fax: +82-2-2001-2199
E-mail: jy7.shim@samsung.com

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Introduction

Mycoplasma pneumoniae is a common etiology of pediatric community-acquired pneumonia (CAP), causing 10%–40% of cases and representing an even higher incidence during epidemics[1]. Epidemics of *M. pneumoniae* infection tend to cycle every 3–4 years. Earlier epidemics until 1996 peaked during summer, while since 2000 epidemics peaked in the fall or early winter in Korea[2]. Korea Centers for Disease control and Prevention identified the annual incidence of *M. pneumoniae* infection in respiratory disease was less than 10% of cases of CAP in 2009, 20.5% in September 2010, however, from July in 2011, the number of cases of *M. pneumoniae*-associated CAP had steeply increased and reached a record high of 62.5% in September 2011[3].

Although *Mycoplasma pneumoniae* pneumonia (MP) is usually a benign, self-limited disease and usually treated effectively with a macrolide, it can develop into a severe, life-

threatening pneumonia in pediatric cases. Refractory MP is defined as a case with prolonged fever accompanied by the deterioration of radiological findings despite appropriate treatment with macrolide[4,5]. In cases of refractory MP in children, a steroid therapy has been reported to be efficacious and well tolerated[1,4].

Several studies have suggested that atopic sensitization or asthma is a risk factor for severe lower respiratory infections[6-9]. However, to our knowledge, there has been no data showing relationship between refractory MP and atopic sensitization or asthma. In this study, we compared clinical features and laboratory characteristics between children with MP responding to macrolide and those with refractory MP, and evaluated the risk factors for refractory MP.

Materials and methods

1. Study subjects and design

We enrolled 203 children who were hospitalized with MP at the Department of Pediatrics, Kangbuk Samsung Medical Center from June to November 2011. In all cases, MP was diagnosed on the basis of radiologic findings and confirmed by serologic testing. Pneumonia was diagnosed as the presence of consolidation on a chest x-ray determined by two pediatric radiologists at the time of admission. We classified pneumonia as lobar or bronchopneumonia, with or without pleural effusion. Infection with *M. pneumoniae* was confirmed by a 4-fold increase in the serologic titer of antimycoplasma antibody (AMA) during the convalescent phase compared to AMA titer drawn during the acute phase, or by an initial AMA titer greater than 1:1280. The AMA titer was measured using an indirect microparticle agglutination method (Serodia-Myco II, Fujirebio, Tokyo, Japan). Other viral studies were not performed during this period.

We analyzed the medical records for patient characteristics including age, sex, duration of hospitalization and fever, family history of allergic diseases, and history of doctor's diagnosis of atopic dermatitis, allergic rhinitis, or asthma in his/her lifetime. The severity of respiratory illness was evaluated based on the extent of pulmonary consolidation, pleural effusion, and supplemental oxygen requirements as defined by oxygen saturation below 90 % in room air, which was measured by pulse oxymetry.

All children who were diagnosed with MP were treated with macrolide antibiotics as well as broad spectrum antibiotics, because coinfection of other bacteria could not be ruled out. Refractory MP was defined as a case with persistent fever over 38.3℃ and a progressive pulmonary consolidation or pleural effusion despite appropriate macrolide antibiotics for 5 days or longer after admission. For the refractory cases, oral prednisolone (1 mg/kg/day) or intravenous methylprednisolone (1 mg/kg/day) was administered in addition to a macrolide antibiotic on the fifth day after admission.

We compared clinical features, laboratory tests, history of allergic diseases, and atopic sensitization rate between children with MP responding to macrolide and children with refractory MP.

This study was approved by The Institutional Review Board of the Kangbuk Samsung Medical Center.

2. Laboratory tests

Blood samples were analyzed for white blood cell count, lymphocyte, hemoglobin, platelet, lactate dehydrogenase (LDH), C-reactive protein, erythrocyte sedimentation rate, total eosinophil counts, titer of AMA and cold agglutinin, total immunoglobulin E (IgE) and allergen-specific IgE antibody. Serum total IgE and specific IgE levels to eight common aeroallergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat, dog, Alternaria, cockroach, tree pollen mixture, and weed pollen mixture) were assayed using ImmunoCAP (Pharmacia Diagnostics, Uppsala, Sweden). Atopic sensitization was defined as $\geq$0.35 IU/mL of at least one specific IgE level[10,11].

3. Statistical analysis

Statistical analysis was performed using STATA release 11.1 (StataCorp LP, College Station, Texas, USA). Differences between two groups were analyzed using Student t test or chi-square test according to the characteristics of variables. Quantitative variables are expressed as means±standard deviation or median values with interquartile range (IQR). The analysis was conducted by transforming the data to a logarithmic scale when data had skewed distributions. Logistic regression was used to determine risk factors associated with refractory MP. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were derived after adjusting for age and sex. A value of P<0.05 was considered statistically significant.

Results

1. Clinical and laboratory characteristics of MP

The clinical and laboratory characteristics of children with MP are shown in Table 1. A total of 203 children were diagnosed with MP. The median age of patients was 5 years (IQR, 3.0–7.0). Twenty-six children (12.8%) were treated with steroids. Mean duration of steroid therapy was 5.4 days and all the patients with refractory MP became afebrile within 24 hours after steroid therapy was started except for 1 case. The female patient with severe refractory MP showed massive left lower lobar consolidation with pleural effusion (Fig. 1A). On the 2nd admission day, she became dyspneic with oxygen saturation of 88%, so we started oxygen supplement

and inserted chest tube. Fever and productive cough continued for the 5 days after admission. On the fifth day, we initiated methylprednisolone therapy (1 mg/kg/day). After two days after the initiation of steroid therapy, body temperature started to be reduced below 38℃ and dyspnea was resolved. Chest radiograph demonstrated decreased consolidation and pleural effusion on the left lower lobe (Fig. 1B). She was discharged on the 26th day of admission without sequelae (Fig. 1C). There were no adverse events observed with steroid therapy. Fourteen children were administered oral prednisolone and intravenous methylprednisolone was given to twelve of them. Seven children (3.4%) were hypoxic at initial presentation and required supplemental oxygen. However, none of the patients were required transfer to an intensive care unit or needed mechanical ventilation. Sixty-eight children (33.5%) had lobar pneumonia, and 135 children (66.5%) showed bronchopneumonia. Pleural effusion was present in 21 children (10.3%) and five of them required chest tube insertion and drainage. Patients demonstrated mild elevated C-reactive protein level and erythrocyte sedimentation rate. The prevalence of previous history of asthma or allergic rhinitis was 7.8% and 36.4%, respectively. The overall atopic sensitization rate was 21.6%.

Table 1. Clinical and laboratory characteristics of pediatric patients hospitalized with *Mycoplasma pneumoniae* pneumonia (n=203)

Characteristic	Value
Age (yr), median (IQR)	5.0 (3.0–7.0)
Male sex	101 (49.7)
Steroid treatment	26 (12.8)
Duration of steroid therapy (day)	5.4±3.8
Oxygen treatment	7 (3.5)
Type of pneumonia	
Bronchopneumonia	135 (66.5)
Lobar pneumonia	68 (33.5)
Pleural Effusion	21 (10.3)
Atopic sensitization	44 (21.6)
Previous history	
Asthma	16 (7.8)
Allergic rhinitis	74 (36.4)
Atopic dermatitis	41 (20.2)
Family history of allergic diseases	86 (42.4)
White blood cell count (/mm)	8,934±4,620
Hemoglobin (g/dL)	12.4±0.9
Platelet count ($\times10^3$/mm^3)	323±121
Lactate dehydrogenase (IU/L)	594±198
C-reactive protein (mg/mL)	2.7±0.2
Erythrocyte sedimentation rate (mm/hr)	36.5±16.4
LogIgE (IU/mL)	4.64±1.48
LogTEC (/mm^3)	4.75±1.19

Values are presented as number (%) or mean±standard deviation unless otherwise indicated.
IQR, interquartile range; LogIgE, logarithmic transformation of immunoglobulin E; LogTEC, logarithmic transformation of total eosinophil count.

2. Comparison of clinical and laboratory characteristics between children with and without refractory MP

We compared the clinical and laboratory findings between children with refractory MP and those with macrolide-responsive MP (Table 2). Children with refractory MP showed higher serum LDH levels and longer duration of hospitalization compared to children who with macrolide-responsive infections. The 26 children who received steroid therapy were hospitalized for a mean duration of 8.5 days, with the longest being 26 days, which would represent more severe pneumonia in children with refractory MP. Blood platelet count was lower in children with refractory MP than in children without. However, the mean age, sex, white blood cell count, lymphocyte count, hemoglobin level, C-reactive protein, erythrocyte sedimentation rate, total IgE concentration, and blood total eosinophil count did not differ significantly between the two groups.

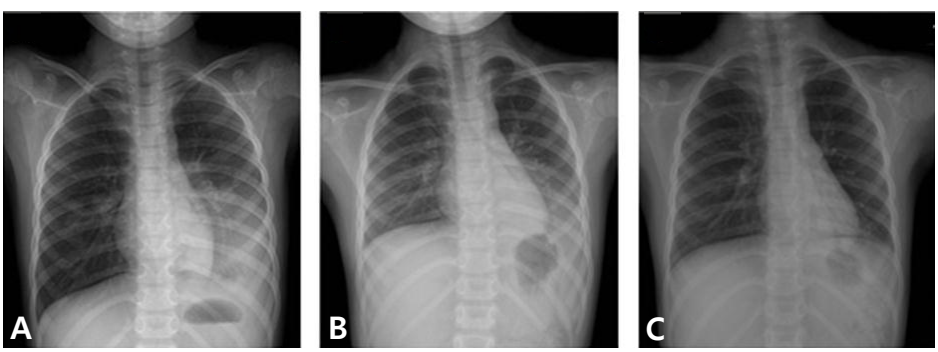

Fig. 1. Radiologic findings in a child with severe refractory *Mycoplasma pneumoniae* pneumonia. Chest radiography showed a massive left lower lobar consolidation with pleural effusion before steroid therapy (A), decreased consolidation with scanty pleural effusion at one week after steroid therapy (B), and cleared consolidation at discharge (C).

3. Comparison of respiratory severity, allergic diseases, and atopic sensitization between children with and without refractory MP

We compared the respiratory severity, type of pneumonia, atopic sensitization, and previous history of allergic diseases between children with refractory MP and those with macrolide-responsive MP. The respiratory severity was investigated on the basis of oxygen requirement, pleural effusion, the number of involved lobes on chest x-ray, and chest tube insertion (Table 3). Children with refractory MP had a higher prevalence of supplemental oxygen therapy and pleural effusion (11.5% vs. 2.3%, P=0.015; 34.6% vs. 6.8%, P<0.001, respectively). There were no significant differences in type of pneumonia between children with and without refractory MP. However, in children with lobar pneumonia, those with more than 2 lobes involved were more likely to require steroid therapy compared to children with 1 lobe involved (P=0.002). The prevalence of atopic sensitization and history of asthma was higher in children with refractory MP than in children without (42.3% vs. 18.6%, P=0.006; 23.1% vs. 5.7%, P=0.002, respectively). After controlling for age and sex, children with atopic sensitization and history of asthma also showed a higher association with refractory MP requiring steroid therapy (aOR, 3.83; 95% CI, 1.55–9.47; and aOR, 5.40; 95% CI, 1.67–17.45,

Table 2. Comparison of clinical and laboratory characteristics between pediatric patients with refractory *Mycoplasma pneumoniae* pneumonia (MP) and those with macrolide-responsive MP

Variable	Refractory MP (n=26)	Macrolide responsive MP (n=177)	*P* value
Age (yr)	4.7±2.3	5.6±3.2	0.163
Male sex	9 (34.6)	92 (52.0)	0.098
White blood cell count (/mm^3)	8,703±3,421	8,966±4,773	0.997
Lymphocyte (/mm^3)	2,426±1,329	2,660±1,476	0.402
Hemoglobin (g/dL)	12.3±0.8	12.4±0.9	0.690
Platelet count (×10^3/mm^3)	280±81	331±125	0.046
Lactate dehydrogenase (IU/L)	725±370	576±154	<0.001
C-reactive protein (mg/mL)	3.4±0.7	2.6±0.2	0.164
Erythrocyte sedimentation rate (mm/hr)	40.6±14.9	34.1±15.5	0.109
LogIgE (IU/mL)	4.89±0.26	4.58±0.22	0.423
LogTEC (/mm^3)	4.65±0.21	4.79±0.09	0.590
Duration of hospital day (day)	8.5±4.1	5.5±2.1	<0.001

Values are presented as mean±standard deviation or number (%).
LogIgE, logarithmic transformation of immunoglobulin E; LogTEC, logarithmic transformation of total eosinophil count.

Table 3. Respiratory severity, atopic sensitization, and history of allergic disease in pediatric patients with refractory *Mycoplasma pneumoniae* pneumonia (MP) and those with macrolide-responsive MP

Valable	Refractory MP (n=26), n (%)	Macrolide responsive MP (n=177), n (%)	*P* value	aOR*	95% CI
Oxygen treatment	3 (11.5)	4 (2.3)	0.015	5.99	1.18–30.41
Type of pneumonia					
Bronchopneumonia	15 (57.7)	120 (67.8)			
Lobar pneumonia	11 (42.3)	57 (32.2)	0.308	2.20	0.90–5.37
No. of lobes in lobar pneumonia					
1 Lobe	6 (54.5)	52 (91.2)			
≥2 Lobes	5 (45.4)	5 (8.8)	0.002	16.57	3.14–87.34
Pleural effusion	9 (34.6)	12 (6.8)	<0.001	13.67	4.22–44.20
Atopic sensitization	11 (42.3)	33 (18.6)	0.006	3.83	1.55–9.47
Previous history					
Asthma	6 (23.1)	10 (5.7)	0.002	5.40	1.67–17.45
Allergic rhinitis	10 (38.5)	46 (26.0)	0.184	2.13	0.88–5.19
Atopic dermatitis	5 (19.2)	36 (20.3)	0.895	0.93	0.32–2.68
Family history of allergic diseases	13 (50.0)	73 (41.2)	0.320	1.45	0.68–3.12

aOR, adjusted odds ratio; CI, confidence interval.
*Adjusted for age and gender.

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respectively). However, there were no associations discovered between refractory MP and allergic rhinitis or atopic dermatitis.

Discussion

In this study, the prevalence of refractory MP requiring steroid therapy was 12.8%. MP is the most common community-acquired pneumonia in school children and is usually responsive to treatment with macrolide antibiotics. However, recently, macrolide-resistant *M. pneumoniae* (MRMP) strains have been identified in epidemics in Far East Asian countries, including Japan, China, Korea, and other countries[12-15]. The strains have mutations in the 23S rRNA[12,13,16,17]. As empirical use of macrolides for lower respiratory infections has become more widespread, MRMP has increased rapidly in recent years[18]. In Korea, a recent study found that the prevalence of MRMP increased significantly over the 4 consecutive epidemics during 2000–2011. Although Macrolide resistance remained low until the 2003 epidemic, MRMP then increased to 14.7% during the epidemic of 2006 and to 56.1% during the epidemic of 2010–2011[19]. Pneumonia caused by MRMP shows an increased duration of symptoms and requires a longer antibiotic treatment course compared to pneumonia caused by macrolide-responsive MP in pediatric patients[17]. Refractory MP may be related to the emergence of MRMP[12]. We cannot speculate on the prevalence of MRMP in this study, because we did not isolate MP strains.

In this study, all patients with refractory MP responded well to steroid therapy, each experiencing an improved clinical course within 24 hours except for 1 case. An exuberant host immune response, which promotes the release of cytokines and a Th1-mediated immune response, may contribute to severe pulmonary injury in some cases of MP[4]. It is suggested that MP is related to mononuclear cell infiltration into the airway, mainly composed of CD4+ T cells[20], which contributes to substantial amplification of the immune response and subsequent injury to lung parenchyma[21]. Corticosteroids, a potent anti-inflammatory agent, have a substantial capacity to mitigate cell-mediated host immune response. Several studies have reported on the efficacy of steroid therapy in children who were nonresponsive to macrolide antibiotics and showed progressive disease[1,4,12,15,22]. Consistent with previous reports, most of patients treated with steroids in our study became afebrile within 24 hours, and showed clinical and radiological improvement without complications. In an animal study using a murine model, the use of systemic steroids combined with antimicrobial therapy is more efficacious in reducing levels of cytokines and chemokines as well as lung inflammation compared to antibiotic or steroid treatment alone[23]. Vascular endothelial growth factor (VEGF) has been proposed as a mediator that may be associated with more severe pneumonia, such as lobar pneumonia with pleural effusion[24]. Dexamethasone has been shown to suppress VEGF release significantly[25]. In this study, children with refractory MP had a higher risk of pleural effusion and lobar pneumonia affecting more than two lobes, which suggests that refractory MP may be related to elevated VEGF levels. Although the mechanisms underlying the effects of steroids remain to be elucidated, the use of steroids is presumed to diminish the host immune response, including mediators like VEGF, in severe MP.

We demonstrated that the prevalence of refractory MP was higher in the patients with asthma or atopic sensitization. Several studies have shown that viral respiratory infections induce more severe symptoms in allergic patients than in normal subjects[6-9]. In an experimental rhinovirus challenge study, exposure to rhinovirus resulted in persistent upper and lower respiratory symptoms in young asthmatic adults with atopic sensitization in contrast to nonatopic ones[7]. We also demonstrated that the prevalence of refractory MP was higher in children with a history of asthma or atopic sensitization, which suggests that a history of asthma or atopic sensitization can be a risk factor for developing refractory MP requiring steroid therapy. In a recent study, the serum levels of VEGF and interleukin (IL) 5 were higher in atopic children with MP compared to non-atopic children[8]. In one in vitro study, IL-4, a Th2 cytokine, was shown to promote VEGF release from airway[26]. Therefore, it is hypothesized that atopic children may be more prone to develop severe pneumonia secondary to IL-4-induced VEGF release.

In the present study, asthma was associated with refractory MP requiring steroids, while neither allergic rhinitis nor atopic dermatitis showed any such association. In contrast to our data, another study showed that atopic conditions other than asthma were associated with an increased risk of severe pneumococcal disease. However, that study did not investigate the relationship between atopic sensitization and severe pneumococcal disease[9].

In this study, serum LDH levels were higher in children with refractory MP requiring steroid therapy than in children with macrolide-responsive MP, while other inflammatory markers queried, such as leukocyte counts, C-reactive protein, erythrocyte sedimentation rate did not demonstrate any difference between the two groups. Previous studies similarly showed that serum levels of LDH increased in patients with refractory MP[12,22]. LDH is a cytoplasmic enzyme present in all major organ systems including the brain, kidney, liver, myocardium, and lung. When cell lysis occurs, or cell membranes are damaged, LDH are released into the extracellular space. Therefore, LDH can be measured as a surrogate marker for tissue breakdown[27]. Other studies have shown that a high serum level of LDH is a prognostic factor for patients admitted to intensive care units with severe pneumonia secondary to the pandemic 2009 influenza A (H1N1), as well as an indicator for the diagnosis of Pneumocystis jiroveci pneumonia[28-30]. We propose that LDH may be used as an indicator of refractory MP,

although further studies are needed to confirm the usefulness of serum LDH levels as an indicator for severity of MP and the need for steroid therapy.

In this study, we defined a *M. pneumoniae* infection as an initial AMA titer greater than 1:1280. Generally, *M. pneumoniae* infection was diagnosed by a 4-fold increase in the serologic titer of AMA during the convalescent phase compared to the acute phase or a single AMA titer greater than 1:640[31,32]. In Korea, a small epidemic of *M. pneumoniae* infection had been occurred during September and October in 2010, one year before this study started[3]. Therefore, we applied more strict criteria to exclude the effect of previous infection. Actually, three patients among 32 patients with an initial AMA titer of 1:640 were identified as a past infection, because the follow-up titer decreased during the convalescent phase.

Limitations of our study include the small single-institution sample size, lack of biologic markers, and no isolation of *M. pneumoniae* strains to confirm resistant strains. We administered steroid therapy based on the lack of clinical response to macrolide antibiotics. In addition, we could not rule out coinfection with other bacteria or viruses, because we did not perform extensive microbiological tests. And the potential mechanisms underlying the increased risk of refractory MP among patients with asthma or atopic sensitization remain to be determined. However, to our knowledge, this is the first study investigating risk factors for refractory MP related to asthma and atopic sensitization.

In conclusion, asthma and atopic sensitization can be risk factors for refractory MP, and, early steroid therapy should be considered in children who have MP with poor response to macrolide treatment and a history of asthma or atopic sensitization, especially during epidemics of *M. pneumoniae* infection.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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