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ORIGINAL ARTICLE

PREVALENCE OF MYCOPLASMA PNEUMONIAE INFECTION AMONG CHILDREN WITH ACUTE RESPIRATORY TRACT INFECTION: A PROSPECTIVE CASE CONTROL STUDY

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The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all the authors, who have met the requirements for authorship.

ABSTRACT

Background: Mycoplasma pneumoniae has been implicated as a significant etiologic agent of lower respiratory tract infection among children between 6 to 18 years old, however, its prevalence in younger children age 5 years and below appears to be increasing.

Objectives: This study was performed to determine the prevalence, clinical and radiologic features associated with *M. pneumoniae* infection among children 5 years old and below admitted with respiratory tract infection .

Methods: This is a prospective case control study involving children 5 years old and below with signs and symptoms of respiratory tract infection, and were tested for *M. pneumoniae* IgM at the Makati Medical Center and admitted between May 1, 2012 to September 30, 2012. Subjects were children with positive *M. pneumoniae* IgM test (MPP) and controls were children with negative *M. pneumoniae* IgM test (MPN). Clinical, radiologic and laboratory characteristics of MPP and MPN were recorded.

Results: Twenty-one out of 82 (25.6%) subjects were MPP. The male to female ratio was 1:1.05 with a mean age of 34 months. Clinical, radiologic characteristic and laboratory findings between MPP and MPN were not statistically significant.

Conclusion: The prevalence of *M. pneumoniae* infection among the subjects was 25.6%. The clinical finding, radiologic, and laboratory parameters did not distinguish M. pneumoniae infection.

KEYWORDS: Mycoplasma pneumoniae, acute respiratory tract infection, mycoplasma infection

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INTRODUCTION

Acute respiratory tract infection is one of the most common infectious diseases in childhood. Worldwide, it causes substantial morbidity and mortality, with two million deaths each year among children less than 5 years old[1]. It is generally accepted that most children who die of acute respiratory tract infection in developing countries have bacterial pneumonia[2]. Pneumonia is the inflammation of parenchyma of the lungs wherein most common bacterial pathogens are *Streptococcus pneumoniae* and *Haemophilus influenzae*[2,3,4,5]. *Mycoplasma pneumoniae (M. pneumoniae)* has been implicated as a significant etiologic agent of lower respiratory tract infection among children between 6 to 18 years old [2,3,5].

In an outpatient clinic and hospital-based study conducted in 1984 among Filipino children 5 years old and below living in a periurban slum and a middle class neighborhood, *M. pneumoniae* accounted for 8.3% of all cases of acute lower respiratory tract infection in the under 5 years old age group[2]. Our recent Philippine Pediatric Society database showed that from January 2011 to January 2012, there were 152 *M. pneumoniae* infections reported, of which 66% belong to the 4 years old and below age group. Prevalence of *M. pneumoniae* in younger children who are 5 years old and below, that was once considered rare, appears to be increasing.[7] Although the infection is endemic in most countries, epidemics occur in four to seven years cycles[6,8]. In the United states, *M. pneumonia* accounted for 15-20% of all pneumonias in 2008[3,8].

The mycoplasma are among the smallest free living organisms which are pathogenic in man[6]. They are deformable rods which pass through bacterial filters and are not seen on gram staining[6].

This bacterial pathogen is not sensitive to penicillin, which is currently recommended for treatment of lower respiratory tract infection in developing countries[3]. Macrolides have shown equal efficacy with amoxicillin in treating pneumonia[2-3]. Considering the growing prevalence of *M. pneumoniae* infection in the younger age groups, macrolides may be necessary in the treatment of community acquired pneumonias (CAP) in infants and children who are 5 years old and below. The objective of this study was to determine the prevalence of *M. pneumoniae* infection among children 5 years old and below who were admitted for respiratory tract infection at the Makati Medical Center (MMC) from May 1, 2012 to September 30, 2012. Specifically, the clinical and radiologic features of respiratory tract infections of the subjects who had positive *M. pneumoniae* immunocard IgM result and those who had negative *M. pneumoniae* immunocard IgM result were compared.

METHODS

This prospective case control study utilized clinical and diagnostic data of children 5 years old and below who were admitted at the Makati Medical Center after showing signs and symptoms of respiratory tract infection from May 1, 2012 to September 30, 2012.

Cases were patients who showed at least two of the following symptoms and were tested positive for *M. pneumoniae* Immunoglobulin M (IgM) using the Immunocard Mycoplasma Enzyme Immunoassay (EIA):

- fever (body temperature 37.8^{0}C and above);
- cough;
- physical findings consistent with a respiratory tract infection:
- chest retractions, cyanosis, sputum production, percussion dullness;

Table 1. Age and gender of study population (n=82)

Age (months)	Gender		Total	M. pneumoniae IgM positive (MPP)	M. neumoniae IgM negative (MPN)	p value
	Male	Female				
0-6	1	1	2	0	2	0.42
7-12	6	5	11	2	9	0.42
13-24	6	10	16	1	15	0.22
25-36	10	9	19	4	15	0.67
37-48	7	5	12	7	5	0.13
49-65	13	9	22	7	15	0.25
Total	42 (48.8%)	40 (51.2%)	82 (100%)	21 (25.6%)	61 (74.4%)	

- aucultatory findings: crackles and wheezing; and
- infiltrates on chest radiograph.

Patients who were treated before with macrolides or hospitalized in the past three months were excluded from the study population.

Controls were the patients admitted at MMC who have the same characteristics as the cases except that they tested negative for Mycoplasma IgM.

Database on age and gender; symptomatology such as presence of fever, cough, tachypnea and chest retractions; auscultatory findings such as crackles and wheezing; laboratory results such as leucocytosis, segmenter predominance and platelet count; presence of oxygen desaturation of less than 95%; and presence of comorbidity such as asthma, were recorded in the study. Similar data were obtained from controls.

Other diagnostics performed in the study included complete blood count and chest radiograph. The latter was performed on all the subjects except for 5 patients. Medications were administered at the discretion of the treating physician. The patients were followed-up in the ward until they were discharged, and the length of hospital stay was noted.

Sample Size Determination: The sample size was computed using Epi info 6.04d (CDC, Atlanta, GA) with 95% confidence interval, power of 80%, with a case-control proportion of 2:1. The minimum number of samples was 63, with a minimum of 21 cases and 41 controls.

Statistical analysis: Statistical analysis was performed using Epi info version 6.04d (CDC, Atlanta, GA). Prevalence of *M. pneumoniae* was estimated with 95% confidence interval. The risk factors were analyzed using Chi square test, Fischer's exact test of independent T test and Kruskal-Walls test, whichever was appropriate. P-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 262 patients were admitted at MMC for respiratory tract infection between May 1, 2012 to September 30, 2012. 82 patients were tested for *M. pneumoniae* IgM. All 82 patients met the inclusion criteria and were enrolled in the study. Among the 82 children, 21

(25.6%) patients tested positive for *M. pneumoniae* IgM (Table 1).

Table 2. Clinical, radiologic and laboratory findings of MPP and MPN (n=82)

Variables	*M. pneumoniae* IgM positive N=21	*M. pneumoniae* IgM negative N=61	p-value
Fever	21 (100%)	61 (100%)	1.00
Cough	21 (100%)	61 (100%)	1.00
Tachypnea at admission	5 (23.8%)	10 (16.3%)	0.32
Retractions at admission	4 (19%)	13 (21.3%)	0.54
Auscultatory findings pneumonia	18 (85.7%)	48 (78.6%)	0.36
Oxygen desaturation O2 sat < 95%	3 (14.3%)	3 (4.9%)	0.15
With history of asthma	5 (23.8%)	10 (16.3%)	0.32
Mean WBC 10^9/L	12.67	11.12	0.33
Mean PMN %	51.9	62.9	0.15
Mean Platelet count 10^9/L	335.33	316.45	0.38
Chest X-ray			
Bilateral infiltrates	5	20	0.89
Infiltrates in right lower lung	7	12	0.42
Infiltrates in left lower lung	0	4	0.40
Atelectasis	1	2	0.56
Length of hospital confinement	3.9	4.7	0.20

WBC – white blood cell count, PMN-polymorphonuclears or segmenters, CXR-chest x-ray, RLL- right lung field, LLL-left lung field

As tabulated in Table 1, the male to female ratio was 1:1.05,and the mean age was 34 months. Barlett's test for homogeneity of variance showed a p-value of 0.85 indicating no significant difference in age and gender between *M. pneumoniae* infection cases (MPP) and controls (MPN).

The 82 subjects presented with fever and cough. Tachypnea on admission was seen on 5 (23.8%) *M. pneumonia*-IgM-positive patients (MPP) and 10 (16.3%) on *M. pneumonia*-IgM-negative patients (MPN). Retractions were appreciated in 4 (19%) MPP and 13 (21.3%) in MPN. Auscultatory findings consistent with pneumonia were appreciated in 18 (85.7%) subjects with MPP and in 48 (78.6%) subjects with MPN. Oxygen desaturation was seen in 3 (14.3%) with MPP and in 3 (4.9%) with MPN. History of asthma was noted in 5 (23.8%) with MPP and in 10 (16.3%) with MPN. The mean WBC was 12.67 10^9/L in those MPP and 11.12 10^9/L in those with MPN. Mean PMN of 51.9% was recorded in those with MPP and in 62.9% with MPN. Mean platelet count was 353.33 10^9/L among those with MPP and 316.45 10^9/L among those with MPN. Among 82 subjects, 5 (6%) did not have chest x-ray at the discretion of the attending physician. 49 (59.8%) were radiologically diagnosed with pneumonia. Out of the 21 MPP, 12 (57.1%) were radiologically diagnosed with pneumonia with one having accompanying atelectasis, 6 (28.5%) had normal chest xray findings and 3 (12.5%) did not have a chest xray. Among those with radiologically diagnosed pneumonia, 5 (41.6%%) had bilateral infiltrates, 7 (58.3%%) had right lung field infiltrates and none had infiltrates in the left lung field. The average length of hospital stay was 4 days for both MPP and MPN. There were two mortalities, both of which were MPN. The epidemiological, clinical and radiological characteristics of patients with MPP and MPN are summarized in table 2. There were no statistical differences in the above mentioned characteristics.

DISCUSSION

The study result showed a 25.6% prevalence of *M. pneumoniae* IgM positive (MPP) among the study population. Based on the variables studied, there was significant difference noted between case and control groups. Neither clinical, radiologic and/or laboratory parameters ed *M. pneumonia* infection from other etiologies.

Based on literature, the prevalence of MPP among younger population ranges between 2.6% [(9)] to 60% [(10)] (Table 3). Our study result showed a figure on the median bracket within this range. There were several reports in literature which studied the same age group. In our country, a study in an outpatient clinic and hospital-based study conducted in 1984 among Filipino children 5 years old and below living in a periurban slum and a middle class neighbourhood, *M. pneumoniae* accounted for 8.3% of all cases of acute lower respiratory tract infection in the under 5 years old age group[2]. One unpublished study also done in the Philippines reported a prevalence of 22% among 1 to 18 years old and 31% belonged to the 5 years old and below age group[11]. Two other reports done in Italy which included subjects within the age group of 5 years old and below showed comparable prevalence of 21.3% and 33%[12,13]. Another 2 studies done in Italy and Finland also showed a prevalence of 20% among 0 to 5 years old age group[8, 14]. In Korea, a study conducted in children 3 months to 14 year old showed higher prevalence of 57% among 3 months to 5 years old[15]. A study done in Papua New Guinea showed higher prevalence of 49% MPP among children who were 6 months to 2 years old[16]. In the Netherlands, a study conducted among 0 to 60 years old and among the 0 to 4 years old MPP showed a lower prevalence of 2.6%[9]. A low prevalence of 3.6% was also reported in a study done in Thailand[17]. This wide range of MPP prevalence underscores the importance of geographic differences and the need for local surveillance studies.

Gender had no significant association with the prevalence of MPP in this study which showed a male to female ratio of 1:1.05. This was comparable to a study done in Italy[12] and Korea[15] which had a 1:1.02 and 1:1.1 ratio, respectively. In a study done in Thailand, male to female ratio varied by age; among children and adolescents the incidence was significantly higher among boys than girls[17].

Our study showed that no epidemiological, clinical and/or radiologic characteristic can predict *M. pneumonia* infection. There were no significant differences between the case and control groups with the factors studied. Fever and cough were present in all MPP and MPN patients. Tachypnea, retractions and auscultatory findings consistent with pneumonia were observed more on MPN but this was not statistically significant. In a study done by Oron et al, the above mentioned clinical factors also showed no significance except for the appreciation of auscultatory findings consistent of pneumonia[8]. Studies by Esposito et al and Principi et al also showed that no clinical finding or laboratory parameter would differentiate *M. pneumoniae* infection however *M. pneumoniae* infection may have a more complicated course if not treated with an appropriate antimicrobial agent[11,12]. In a case report by Kumar et al, *M. pneumoniae* infection presented as a non-resolving pneumonia in a neonate who was febrile, hypoxic, tachypneac with subcostal and intercostal retractions [18]. This incident may play an important role in always considering *M. pneumoniae* as one of the etiologic agents of a pneumonia that would not resolve in younger population despite treatment with penicillin-based antimicrobial agent. This may also justify the use of macrolide as the first line of treatment.

Table 3. Prevalence of Mycoplasma infection in literature

Authors	Year published	Country	Age Group	Setting	Sample size	*M. pneumonia* Infection (%)	Clinical findings	Laboratory Examination	Radiologic Findings
Comendador et al	unpublished	Philippines	1 to 18 years	Hospital	21	28% 60% age under 5	Fever, cough, coryza, wheezes, retractions	CBC, ESR EIA	CXR interstitial pneuamonia, bilateral infiltrates
Dorigo-Zetsma et al	2001	Netherland	Birth to 60 years	Hospital	1172 114 (0-4 yrs old)	2.6%	Cough, fever, rales, tachypnea, rhonchi	PCR	CXR: Linear opacities, reticulonodular infiltrates, lobar consolidations
Esposito et al	2001	Italy	2-14 years	Hospital	203	33% mean age 3-6 years	Cough, fever, rales, tachypnea	CBC WBC, SEG, CRP and ESR PCR	CXR: Perihilar linear opacities, reticulonodular infiltrates, lobar consolidation
Garcia et al	2004	Philippines	1 to 15 years	hospital	142	60% age under 5	Fever, coryza, headache, dry cough	Throat swab culture, mycoplasma agglutination test	CXR interstitial infiltrates and hilar
Hadi et al	2011	Iran	6 to 17 years	Hospitial	100	10%	Symptoms of lower respiratory tract infection	CBC PCR	CXR consistent of pneumonia
Jinho yu et al	2005	Korea	0 to 15 years	hospital	0-3:417 4-6:508 7-15:394	Low titer on 0 to 3 age group	Symptoms of lower respiratory tract infection	CBC, Ab titer – indirect agglutination particle test	
Kumar et al	2010	India	18 days old	Hospital	1	Case report	fever, hypoxia (82% O2sat), tachypnea, retractions	CBC, CRP EIA	CXR: lobar consolidation CT: lobar consolidation with minimal left-sided pleural effusion
Liu Chun-ling et al	2010	China	2 to 14 years	Hospital	635	45.7% 33.3% age 2-5 years	Acute respiratory infection criteria	Serum Ab test Ab titer test	-

Oron et al	2006	Israel	1 to 18 years	ER	100	20% age 0 to 5 years	Fever, cough, coryza, wheezing, physical findings consistent of pneumonia	CBC WBC SEG, PLT, Serologic Ab study	CXR: bilateral, multiple, alveolar infiltrates, atelectasis
Phares et al	2007	Thailand	Birth to 70 years	Hospital	755	3.6%	Acute respiratory tract infection criteria	Serologic Ab study, PCR	-
Principi et al	2001	Italy	2-14 years	Hospital	613	21.3% age 2-4 years	Cough, fever, rales, tachypnea, rhonchi	CBC WBC, SEG, CRP EIA	CXR: Diffuse lobar infiltrates
Saikku Pekka et al	1984	Philippines	3 mos months to 5 years	Hospital	318	8.3%	Acute respiratory tract infection criteria	EIA	-
Samson et al	unpublished	Philippines	1 to 18 years	Outpatient clinic and hospital	58	22% 31% age under 5 years	Symptoms of lower respiratory tract infection	Mean WBC: 7.2 cells/mm^3 Mean ESR, Female: 65.2mm/hr Male: 43 mm/hr EIA	CXR: interstitial and lobar pneumonia
Shann et al	1986	Papua New guinea	6 mos to 2 years	Hospital	94	49%	Cough, fever, rales, tachypnea, rhonchi	CFT	CXR: Linear opacities, reticulonodular infiltrates, lobar consolidation
Waris et al	1998	Finland	1 month to 16 years	Outpatient clinic and hospital	261	21% age under 5 year	Acute respiratory tract infection criteria	EIA	CXR consistent of pneumonia
You-souk Youn et al	2010	Korea	3 mos to 14 years	Hospital	191	57% age 3mos to 5 years	Cough, fever, rales, tachypnea	Microparticle agglutination test, PCR	CXR: Inc nodular densities along bronchial tree Lobar consolidation

In this study, a positive history of asthma was not significantly different between the two groups. Some literature has suggested that infection with *M. pneumoniae* may precede the onset of asthma or exacerbate asthma symptoms [19]. In a study done by Zaki et al, *M. pnemoniae* is a common bacterial pathogen associated with acute exacerbations of asthma in children 15 years or older[19]. In an Israeli study by Oron on children 5 years old and below, history of asthma was not significantly found to be a predictor for MPP, as was seen in this study. In a Korean study which evaluated levels of vascular endothelial growth factor (VEGF) and interleukin (IL)-5 among MPP patients with asthma, the serum levels of VEGF and IL-5 were more increased in atopic children with *M. pneumoniae* pneumonia, suggesting that these cytokines may act through their respective pro-inflammatory pathways to aggravate the allergic status and induce airway hypersensitivity during *M. pneumoniae* pneumonia in atopic children[20].

This study showed that the mean WBC count of 12.6 10^9/L, mean segmenter count of 51.9%, and mean platelet count of 353.3 10^9/L were not significantly different between the two groups. Mean values of the factors mentioned among MPP and MPN where within normal limits for same age reference. Oxygen desaturation also showed no statistical association. A study by Oron et al in which subjects were of the same age group like in this study, similar findings were noted[8]. The laboratory parameters were also not significantly different between case and control groups in studies done by Liu Chun-ling et al, Youn et al and Principi et al[13,15,21]. However an additional finding noted by Youn et al was that lymphopenia may be a characteristic of MPP in the acute stage, while thrombocytosis was seen in 8% of patients upon admission[15]. This is in contrast to an unpublished study done in the Philippines by Samson et al wherein the mean WBC count (7.210^9/L) is in the lower bracket of normal range and was statistically significant. However, WBC counts of the two groups were within normal values for same age reference[1)].

Chest radiograph findings in this study showed no significant differences between the two groups. Studies done locally[10,11,21] and abroad[8,9,12-16,19,22]described chest radiograph as perihilar or linear infiltrates, lobar consolidation, pleural effusion and atelectasis; however, none showed significant association as compared to MPN.

In the 2010 Cochrane Collaboration for antibiotics used in lower respiratory tract infections (LRTI) secondary to *M. pneumoniae* in children, one study of children with LRTI secondary to atypical bacterias diagnosed by polymerase chain reaction or paired sera found that children treated with azithromycin had significantly better clinical success rates on follow up versus the placebo[23].

The average length of hospital stay was four days for both case and control groups. This is comparable to a study by Principi wherein the range of length of hospital stay was 4-8 days[13]. The clinical course of *M. pneumoniae* infection is typically mild; however, there were several case reports of severe complications following *M. pneumoniae infection* with considerable morbidity and mortality. A study done by Kim et al showed that a considerable proportion of children with *M. pneumoniae* infection were at risk for developing small airway obstruction[24]. In Australia, Sabato et al noted that subjects with previous *M. pneumonia infection* had abnormal mean forced expiratory volume in one second and forced expiratory flow after 50% of the expired vital capacity, compared with 64 healthy controls. These findings indicate impaired function three years after initial infection[25].

LIMITATIONS

Out of the 262 patients admitted with respiratory tract infection during the study period, only 82 (32%) were tested for IgM *M. pneumoniae* since the testing was left to the discretion of the admitting physician. The diagnosis of *M. pneumoniae* infection was made on the basis of a single serology test and it may be positive for as long as six months after the *M. pneumoniae* infection. These biases may underestimate the true prevalence of *M. pneumoniae* infection.

CONCLUSION

The prevalence of *M. pneumoniae* infection among children 5 years old and below with respiratory tract infection who had IgM *M. pneumoniae* test admitted at a tertiary care center in Makati was 25.6%. The clinical, radiologic or laboratory findings did not distinguish *M. pneumoniae* infection.

RECOMMENDATION

This study involved admitted patients with respiratory tract infection who had IgM *M. pneumoniae* test and this bias probably underestimated the true prevalence of *M. pneumoniae* infection. A prospective study is recommended wherein all eligible patients, including the outpatients with respiratory tract infection to be tested for IgM *M. pneumoniae* in order to document the real prevalence of *M. pneumoniae* infection in the younger population.

Long-term follow up of patients is recommended to document possible long term effects of *M. pneumoniae* that were not elicited during the time of confinement.

In diagnosing *M. pneumoniae* infection, it is better to use a paired sera since a 4-fold rise in antibody titer in acute and convalescent sera is considered the gold standard for the diagnosis of current *M. pneumoniae* infection[7]. A significant rise in antibody titer cannot be demonstrated unless the first blood specimen is taken within ten days from the onset of illness or unless convalescent serum is obtained at proper time intervals[7]. The use of PCR is also recommended for diagnosing acute *M. pneumoniae* infections during the first two weeks after onset of illness[26,27].

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