

Association of *Mycoplasma pneumoniae* with Respiratory Tract Infections in Children

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ABSTRACT

Mycoplasma pneumoniae is one of four most common species of organisms that are responsible for most clinically significant infections in humans. It is a frequent cause of acute respiratory infections in both children and adults. The organism can cause pharyngitis, otitis, tracheobronchitis, or community-acquired pneumonia, but patients may also remain totally asymptomatic. Aim of this prospective study for children, was to investigate the association of *M. pneumoniae* with respiratory tract infections in a Saudi population. This study was designed as a case-control study in which 90 patients (Mean age of the patients in case group was 5.94±2.73 and in control group was 6.51±2.26) of either sexes were included. These patients were classified into two groups: first group (case group), included 45 patients who had been admitted in hospital with diagnosis of respiratory tract infections and the second group (control group), included 45 healthy patients who had no history of respiratory tract infections. Both the groups were age and sex matched. Presence of IgM antibodies to *Mycoplasma pneumoniae* was assessed by ELISA technique in both groups. In the case group, 4 (9%) cases out of 45 children were positive for anti-mycoplasma antibody whereas in the control group, all children were negative. All positive case group patients had symptoms of acute pneumonia. 18 (40%) of the patients were diagnosed with bronchial asthma (40%) inclusive of all the four cases diagnosed with *Mycoplasma pneumoniae* infection. The relative risk for the occurrence of mycoplasma infection was estimated to be 9 (95% C.I = 0.49-162.43). However, on comparing the case and control groups, the result was not found to be statistically significant. (Fischer Exact Test p = 0.0583). Children in Saudi Arabia are at a relatively higher risk of developing *Mycoplasma pneumoniae* infection especially those predisposed with underlying chronic respiratory illnesses such as asthma. This is a first study of its kind from the region reporting such a disease in children using a serological assay as ELISA. Further studies are required to evaluate the risk of coinfection by *Mycoplasma pneumoniae*, *Streptococcus pneumoniae* and *Chlamydia pneumoniae*. Evaluating and establishing a correlation between *Mycoplasma pneumoniae* and the onset of asthma among infected children can be a prospective field of study for further knowledge of the role of *Mycoplasma pneumoniae* in chronic respiratory tract infections.

Key words: *Mycoplasma Pneumoniae*, Respiratory Tract Infections, Children

1. INTRODUCTION

M. pneumoniae is well known as an important infectious cause for respiratory system and most cases of mycoplasma respiratory infection occur singly or as

family outbreaks (Baum, 2004). This organism is reported to be the most frequent 'atypical' pathogen responsible for Community-Acquired Pneumonia (CAP) in children and adults (Hammerschlag, 2001; Thibodeau and Viera, 2004). The community-acquired respiratory

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tract infection such as upper respiratory inflammation, bronchitis and a pneumonia, mainly in children and young adults. The literature data concerning the prevalence of *M. pneumoniae* varies greatly from study to study depending on the population and diagnostic methods (Deerojanawong *et al.*, 2006). Until the beginning of 1990, *Mycoplasma pneumoniae* was thought to be a pathogen that causes pneumonia in patients aged more than 5 years and only sporadic associations had been observed between it and respiratory tract infections other than pneumonia (Principi and Esposito, 2001). However and since then, with specialised diagnostic techniques it will allowed a considerable amount of new information to be obtained. In children, it has been seems that *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have a more important role in causing both upper and lower respiratory-tract infections than previously thought; they have been associated with wheezing and seem to be frequent also in children aged less than 5 years (Hammerschlag, 2000; Esposito *et al.*, 2001; Principi *et al.*, 2001; Esposito *et al.*, 2000).

In United States, It was believed that Mycoplasmas to be responsible for 15-20% of all cases of Community-Acquired Pneumonia (CAP) between 1962 and 1975 in Seattle, Washington (Foy, 1993). An serological studies conducted in Denmark, showed a pattern of *M. pneumoniae* infections over a 50-year period from 1946 through 1995 with endemic disease transmission punctuated with cyclic epidemics every 3-5 years (Lind *et al.*, 1997). A number of well-described outbreaks of *M. pneumoniae* respiratory infections in the community and in closed or semi-closed settings such as military bases, hospitals, religious communities, schools and institutions for the mentally or developmentally disabled have been reported. Even though long-term morbidity is uncommon, the acute illnesses are often disruptive and can consume significant resources (Waites and Talkington, 2004). A Finnish study (Korppi *et al.*, 2004), reported that *M. pneumoniae* was detected in 30% of pediatric CAP and in over 50% among children aged 5 years or older, making it the single most common pathogen detected. A study performed in the United States during the 1990s detected *M. pneumoniae* in 23% of CAP in children 3-4 years of age (Block *et al.*, 1995) and in French study (Layani-Milon *et al.*, 1999), documented the occurrence of *M. pneumoniae* in children less than 4 years of age without significant differences in infection rates for other children or adults. These findings may reflect the greater number of young children who attend day care centers on a regular basis than in previous years and the ease with which young children share respiratory secretions

with older household members or contacts (Atkinson *et al.*, 2008) and in other study (Marston *et al.*, 1997), they reported that *M. pneumoniae* was definitely responsible for 5.4% and possibly responsible for 32.5% of 2776 cases of CAP in hospitalized adults in Ohio State. An additional finding of their study was their observation that the incidence of pneumonia due to *M. pneumoniae* in hospitalized adults increased with age and it was second only to *S. pneumoniae* in elderly persons.

In Saudi Arabia, there are very little information concerning the association of *Mycoplasma pneumoniae* with respiratory tract infections in children and in a study of the epidemiology and clinical features that has been conducted by Madani and Al-Ghamdi (2001), they found that infections were more common in infants and preschool children than in school children and young adults of 40 patients with culture-proven infections caused by this organism, Additionally, mortality attributable to *M. pneumoniae* pneumonia was relatively high in patients with comorbidities. Other study (Rashed, 1998), *Mycoplasma pneumoniae* was found to be the second most common causative agent after Respiratory Syncytial Virus (RSV) accounting for 9% of all cases of 511 children with acute respiratory tract infection, In another study (Mohamed and Evans, 1987), the organism was accounted for 6% of all 112 adult patients cases with community acquired pneumonia and in another retrospective study, the organism accounted for 23% of all 567 of pneumonic episodes in adult patients (Kurashi *et al.*, 1992).

Therefore, it seem that it is an important in this prospective study to investigate, the role of *Mycoplasma pneumoniae* and its association with respiratory tract infections in children.

2. MATERIALS AND METHODS

This study was designed as a case-control study, in which 90 patients (Mean age of the patients in case group was 5.94 ± 2.73 and in control group was 6.51 ± 2.26) of either sexes were included. The study conducted during one year (January, 2012-January, 2013) in Pediatric ward at Asser Central Hospital in Abha (a city in southwest region of Saudi Arabia). These patients were classified into two groups: first group (case group), included 45 patients who had been admitted in hospital with diagnosis of respiratory tract infections and the second group (control group), included 45 healthy patients who had no history of respiratory tract infections. Both the groups were age and sex matched. Presence of IgM antibodies to *Mycoplasma pneumoniae* was

assessed by ELISA technique in both groups; Vircell Microbiologists kit for Mycoplasma (Vircel Microbiologists) was used for detection of IgM antibodies to *M. pneumoniae* and a sample with antibody index value of more than 11 was considered seropositive as having IgM specific antibodies against *M. pneumoniae* on manufacturer's guidelines (Vircel Microbiologists). All our information was statistically analyzed by using the Statistical Package for the Social Sciences version 13.0 (SPSS software, Inc., Chicago, IL, USA). SPSS software and for statistic analysis, t-test and chi square test was used. Results

with P value less than 0.05 was considered as statistically significant.

3. RESULTS

Ninety patients were studied. Mean age of the patients in case group was 5.94±2.73 and in control group was 6.51±2.26). There was not significant statistic difference for age between two groups (p = 0.08) and age groups between male and females patients were not statistically different **Fig. 1**.

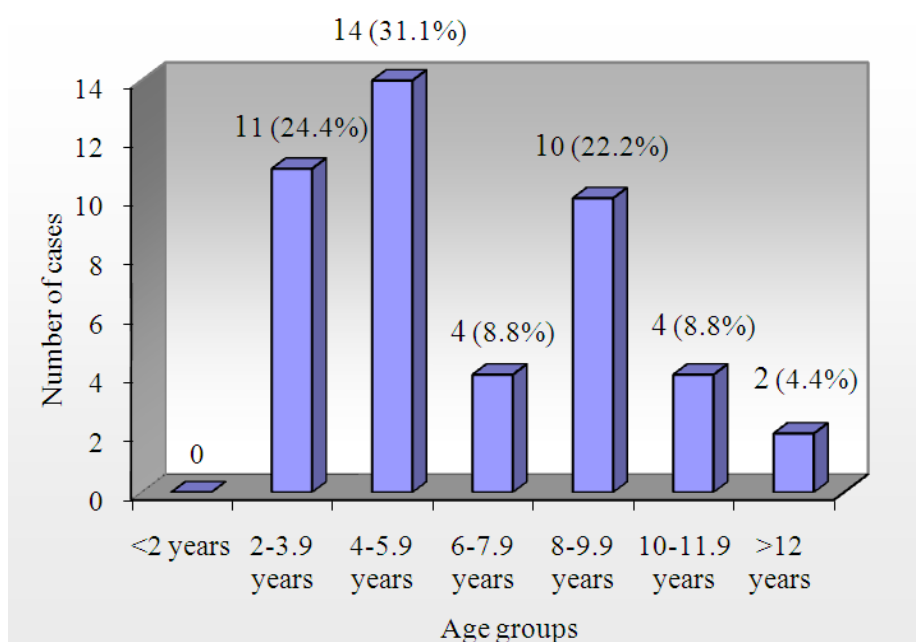


Fig. 1. Age wise distribution of Patients in Case group (n = 45)

Table 1. Antimycoplasma antibody in case and control groups (n = 45; n = 45)

Group	Antimycoplasma ab		Total
	Positive	Negative	
Case	4	41	45
Control	0	45	45

p = 0.0583

In the case group, patients with diagnosis of respiratory tract infections such as pneumoniae and bronchial asthma, 4 (9%) cases out of 45 children were positive for anti-mycoplasma antibody whereas in the control group, all children were negative. All positive case group patients had symptoms of acute pneumonia.

Table 2. Clinical manifestations associated with by *Mycoplasma pneumoniae* infection in case group patients (n = 45)

Variable	Frequency (%)
Type of Infection: Pneumonia	45(100)
Medical illnesses bronchial asthma	18(40)
Symptoms and signs	
Fever	43(96)
Cough	45(100)
Dyspnea	45(100)
Cyanosis	11(24)
Wheeze	18(40)
Crackles	26(58)
Abnormal chest x-ray	25(56)

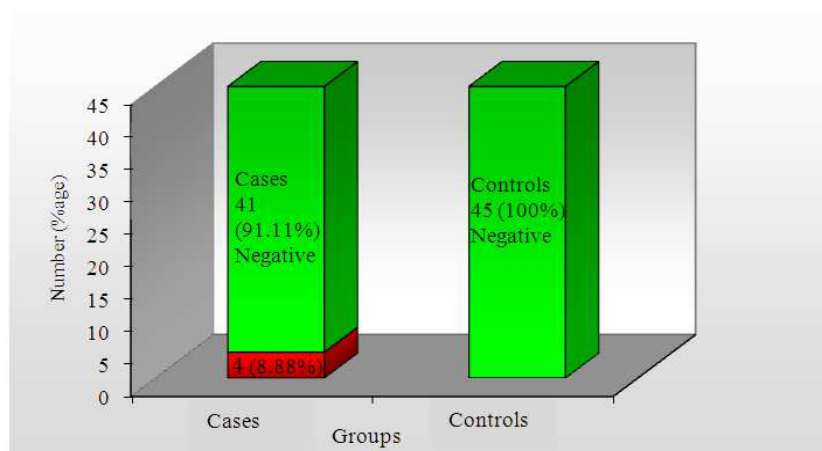


Fig. 2. Percentage of antimycoplasma antibodies in case and control groups (n = 45; n = 45)

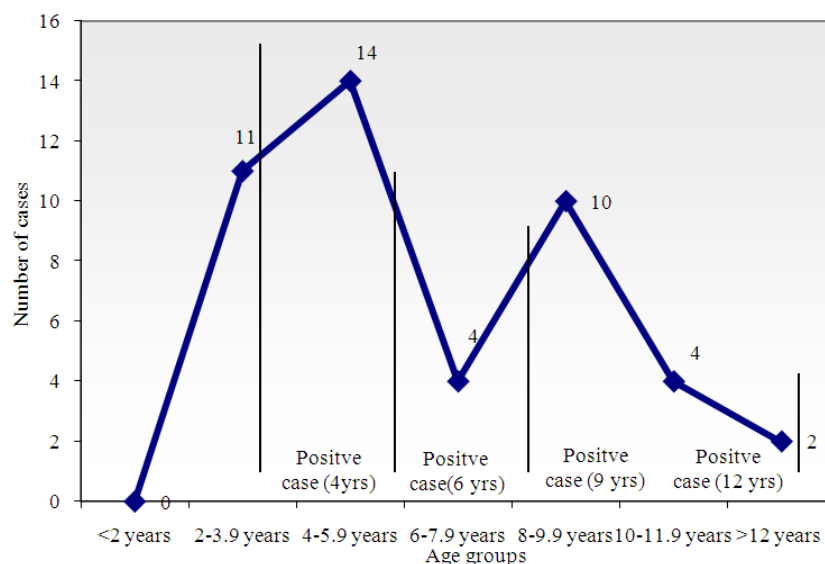


Fig. 3. Age of positives among cases (n = 4)

18 (40%) of the patients were diagnosed with bronchial asthma (40%) inclusive of all the four cases diagnosed with *Mycoplasma pneumoniae* infection (Table 1 and 2). The relative risk for the occurrence of mycoplasma infection was estimated to be 9 (95%CI = 0.49-162.43). However, on comparing the case and control groups, the result was not found to be statistically significant. (Fischer Exact Test $p = 0.0583$, (Fig. 2 and 3).

4. DISCUSSION

Mycoplasma pneumoniae, is a common respiratory pathogen that produces diseases of varied severity

ranging from mild upper respiratory tract infection to severe atypical pneumoniae, although it is rarely fatal, this pathogen is an important cause of acute respiratory tract infection especially as a potential etiology of the clinical entity termed “ atypical pneumoniae” the organism is also responsible for producing a wide spectrum of non-pulmonary manifestations including neurological, hepatic, cardiac diseases, hemolytic anemia, polyarthritis and erythematic multiforme (Kashyap and Sarkar, 2010). The pathogen is out of 17 known human mycoplasmas species, consider as a significant respiratory pathogen in persons of all ages, causing respiratory diseases and it may induce clinically significant manifestations in extra-

pulmonary sites by direct invasion and/or immunologic effects. Macrophage activation, cytokine induction and super-antigen properties are some factors related to the pathogenicity of mycoplasmas (Razin *et al.*, 1998; Waites and Talkington, 2004; Waites *et al.*, 2008).

Many studies were conducted to evaluate the relation between infection of *Mycoplasma pneumoniae* with respiratory tract and to evaluate the relative risk of these agent for respiratory tract infections in populations and for this purpose we conducted this study to recognize the role of infectiou agent and its association to the respiratory tract in children.

In our study the mean age of the patients in case and control groups was 94 ± 2.73 and in control group was 6.51 ± 2.26 . There was not significant statistic difference for age between two groups ($p = 0.08$) and age groups between male and females patients were not statistically different and this will reveal the detection of IgM antibodies to the patients at younger age and confirm the risk of association of the *Mycoplasma pneumonia* in patients with respiratory tract infections, these results in agreement with other studies (Atkinson *et al.*, 2008; Cassell *et al.*, 1996).

In the present study, the relative risk for the occurrence of mycoplasma infection in case group was estimated to be 9 (95% C.I = 0.49-162.43). However, on comparing the case and control groups, there was no statistically significant. (Fischer Exact Test $p = 0.0583$) therefore, it seem the possibility of infection occurrence in cases group was higher in contrast to the control group as no positive cases were detected, thus, children in this country are at a relatively higher risk of developing *Mycoplasma pneumoniae* infection especially those predisposed with underlying chronic respiratory illnesses such as asthma. The association of *Mycoplasma pneumoniae* with respiratory tract infections such as pneumonia will observed in our study for 9% of all cases of children and that will matched with other reported studies (Rashed, 1998).

In our study, the most common clinical manifestation of *Mycoplasma pneumonia* infection was observed in all case group patients including pneumoniae. *Mycoplasma pneumoniae* pneumonia patients present with acute onset of fever (96%), Dyspnea (100%) and cough (100%) in almost all the patients, there were cyanosis (24%), wheezes (40%) and crackles (58%) in some of the patients. After 3 to 7 days onset of constitutional symptoms, cough and radiographic evidence of pneumonia were appeared (56%). Fever ranging from 38°C to 39.5°C were commonly seen. The radiographic findings of *Mycoplasma pneumonia* pneumonia were interstitial pneumonitis and bronchopneumonic patterns

were common. The pathogen had shown an association with bronchial asthma. These symptoms were seen in 18 (40%) of the patients inclusive of all the four cases diagnosed with *Mycoplasma pneumoniae* infection. The study suggested the possible that such an infection may exacerbate the asthma. Although we have limited data regarding prevalence and association of *Mycoplasma pneumoniae* respiratory infection with asthma in this country, However, this study findings was matched with the results reported by other studies that the infection with this organism may precede the onset of asthma and may exacerbate asthma with more difficulty in control of it (Nisar *et al.*, 2007; Brown *et al.*, 2011). In other study conducted by Biscardi *et al.* (2004), it was reported that infection with *Mycoplasma pneumoniae* was a causative microbe in 20% of exacerbations in asthmatic children that requiring hospitalization for asthma exacerbations. They found the children who are predisposed to develop asthma, *M pneumoniae* infection may trigger its onset. The study was suggested that about one half of first severe asthma attacks in children can occur during an infection with *M pneumoniae*. In addition, in children with *M pneumoniae* who are having their first asthma attacks, failure to give macrolides greatly increases the risk of a subsequent severe attack requiring hospitalization or admission to the Intensive Care Unit.

In this study, we assessed the IgM antibodies to *Mycoplasma pneumoniae* infection by ELISA technique; as detection of specific antibody by this assay is a reliable and useful method for diagnosis of *Mycoplasma pneumonia* respiratory disease in human (Cassell *et al.*, 1996), it was found that the method offered several major advantages over other antibody detection methods: objectivity, immunoglobulin class and subclass specificity and increased sensitivity. In comparison study for the efficacy of an IgM and IgG ELISA based on whole organisms of the FH reference strain as the antigen, to that of culture and PCR for the diagnosis of *Mycoplasma pneumoniae* infection in 256 children (2 to 16 years of age, mean 6.3 years) with radiographically confirmed pneumonia, it was found 38 patients who had all three diagnostic tests performed and which were positive by one or more tests, 35 were positive by ELISA and 32 of these were positive by culture, PCR or both. Fourteen of the 16 culturely positives were also positive by ELISA, therefore, it was appeared that ELISA test was more sensitive than culture and comperable in sensitivity to detection of infection by PCR, furrthermore, as 3 out of 35 ELISA positives were negative by other methods, they will suggested that the ELISA was highly specific (Cassell *et al.*, 1996). In other

study, it was found that children and teenagers respond predominantly with IgM antibodies, whereas patients older than 40 years often have an antibodies of IgG detected by ELISA (56% of cases) response only, which probably because of reinfection (Uldum *et al.*, 1992; Cassell *et al.*, 1996). This was also confirmed by our recent study, which will revealed the detection of IgG antibodies to the patients at age older than 60 years (Mean age in case group was 62.54 ± 11.19 and in control group was 64.68 ± 13.65) and it confirmed the risk of association of the *Mycoplasma pneumoniae* infection in patients for Ischemic Heart Disease (Abdul-Wahab *et al.*, 2012).

In the present study, association of *Mycoplasma pneumoniae* with respiratory tract infections in our patients was revealed that the infection with this agent was a risk factor for respiratory tract, however, It should be take in consideration that several other studies described the coinfection between *Mycoplasma pneumoniae* and other bacteria agents such as *Streptococcus pneumoniae* (Toikka *et al.*, 2000) and *Chlamydia pneumoniae* (Principi *et al.*, 2001; Principi and Esposito, 2001), which might occur in patients and may be an important cofactor for respiratory tract infections. The organism should be considered in differential diagnosis of community-acquired pneumonia (Hammerschlag, 2001; Korppi, 2003) and in co-infections, when they are unresponsive to beta-lactams, which are commonly administered. It was concluded that co-infections will prolongs the course of several diseases, including pneumonias (Vervloet *et al.*, 2007). Thus, the study was suggested that as there was no doubt that coinfection by *Mycoplasma pneumoniae*, *Streptococcus pneumoniae* and *Chlamydia pneumoniae* have a more significant role as a causes of respiratory tract infections in children and therefore, it will need further studies to be undertaken.

On the other hand and due to the lack of cell wall, all mycoplasmas are innately resistant to all beta-lactams and glycopeptides. Sulfonamides, trimethoprim, polymyxins, nalidixic acid and rifampin are also inactive (Kashyap and Sarkar, 2010), furthermore although, *Mycoplasma pneumoniae* was susceptible to antibiotic that interfere with protein or DNA synthesis, such as tetracycline, macrolides and quinolones (Waites and Talkington, 2005; Brown *et al.*, 2011), there is a data in literature concerning in recent studies reported of an antimicrobial resistant in *M. pneumoniae* (Kashyap and Sarkar, 2010), In studies that was reported in Japan, macrolide resistance has been emerged (Matsuoka *et al.*, 2004; Morozumi *et al.*, 2005), although the clinical

failure was unlikely (Suzuki *et al.*, 2006), However, It should be take in consideration the role of several factors for detection of *Mycoplasma pneumoniae* infection for diagnosis of *Mycoplasma pneumoniae* respiratory disease in human and that with further clinical studies are needed.

5. CONCLUSION

Our results showed children in Saudi Arabia are at a relatively higher risk of developing *Mycoplasma pneumoniae* infection especially those predisposed with underlying chronic respiratory illnesses such as asthma. This what is apparently the first study performed for *Mycoplasma pneumoniae* reporting such an infection in children using a serological assay as ELISA. Further studies are required to evaluate the risk of coinfection by *Mycoplasma pneumoniae*, *Streptococcus pneumoniae* and *Chlamydia pneumoniae*. Evaluating and establishing a correlation between *Mycoplasma pneumoniae* and the onset of asthma among infected children can be a prospective field of study, for further knowledge of the role of *Mycoplasma pneumoniae* in chronic respiratory tract infections.

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