Value of serum Mycoplasma pneumoniae immunoglobulin in the diagnosis of mycoplasma-related pneumonia in newborns

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Abstract. Mycoplasma pneumoniae (M. pneumoniae) is an important pathogen of neonatal acquired pneumonia in newborns. Rapid and accurate diagnosis of M. pneumoniae infection is critical because timely antibiotic therapy can reduce drug overuse and prevent the development of bacterial resistance. Anti-M. pneumoniae immunoglobulin M (IgM) is an indicator of early infection that can persist for several months. Studies have shown that anti-M. pneumoniae IgA in adults is a reliable indicator of early M. pneumoniae infection. The aim of this study was to assess the association between M. pneumoniae IgA, IgM and IgG in mycoplasma-associated pneumonia. We recruited 80 newborns with pneumonia with potency of serum M. pneumoniae IgM positive or two sera anti-M. pneumoniae IgG increased by 4-fold. The potency of serum M. pneumoniae IgA, IgM and IgG were detected. The initial positive rates of IgM and IgA in M. pneumoniae were 63.6 and 33.8%, respectively, after infection. The positive rate of IgM and IgA in M. pneumoniae increased to 97.5 and 56.3%, respectively, one week after infection. Compared with anti-M. pneumoniae IgA, anti-M. pneumoniae IgM has higher sensitivity in the diagnosis of neonatal mycoplasma-associated pneumonia. Detection of two sera can more effectively improve the diagnostic accuracy.

Introduction

Mycoplasma pneumoniae (M. pneumoniae) is one of the most common pathogens causing pneumonia, especially neonatal pneumonia. The typical clinical manifestation is cough without runny nose, but the symptoms vary widely from asymptomatic respiratory infections to severe pulmonary infections (1). M. pneumoniae is sensitive to macrolide or tetracycline antibiotics, but because of the lack of appropriate diagnostic methods, these antibiotics are not used in a timely manner. M. pneumoniae is also sensitive to fluoroquinolone antibiotics, but fluoroquinolones cannot be used in neonates because of cytotoxic side effects (2). In recent years, the extensive use of macrolide antibiotics has led to the increase of macrolide-resistant M. pneumoniae around the world (3). The proportion of macrolide-resistant M. pneumoniae in Asia is 10-20% (4.5), whereas in some parts of China it is as high as 90%. Therefore, there is an urgent need for a rapid and accurate diagnosis method of M. pneumoniae infection to choose appropriate antibiotics to treat M. pneumoniae-associated pneumonia, thereby reducing the abuse of antibiotics and drug-resistant strains.

Anti-M. pneumoniae immunoglobulin M (IgM) is used to detect acute infection. However, the levels of IgM antibody in blood were too low to be detected in some patients in the early stage of acute infection and in reinfection (6). In addition, the IgM antibody can only be detected several months after infection in the blood of some patients (7). So, the clinical diagnosis of M. pneumoniae infection is very difficult. In the last few decades, only a small number of studies have reported the use of M. pneumoniae IgA antibodies to diagnose M. pneumoniae infection. Reports indicate that detection of anti M. pneumoniae IgA antibodies in adults is more sensitive than IgM in the diagnosis of acute mycoplasma-associated pneumonia (8). However, the sensitivity of M. pneumoniae IgA was low for diagnosing of mycoplasma-associated pneumonia in neonates (9).

The incidence of M. pneumoniae-associated pneumonia is high in neonates, but no studies have reported the clinical value of anti-M. pneumoniae Ig in the diagnosis of M. pneumoniae-associated pneumonia in neonates. The purpose of this study was to assess the clinical significance and efficacy of anti-M. pneumoniae Ig in the diagnosis of M. pneumoniae in neonates.

Patients and methods

Study subjects. We recruited 80 newborns in Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine from May 2013 to June 2016. The cohort included 31 boys and 49 girls. Mean age: 16.6±5.3 months, age ranged from 8-27 days. All newborns had cough and fever. Bronchial
pneumonia or lobar pneumonia was identified in all newborns by chest X-ray. Body temperature was measured with an infrared tympanic thermometer and temperature above 38.0°C was considered as fever. The patients had continued fever (≥38°C) for 4.3±2.7 days before admission (information provided by the relatives of the patients). All patients with *M. pneumoniae* infection showed serum antibody positive or increased antibody potency at least two weeks after the infection: 26 were serum positive, in 72 IgM potency increased 2-fold, and in 31 IgG potency increased 4-fold. The patients involved in this study had no other disease that could alter the clinical disease process. The clinical data of the patients included age, fever duration, length of hospitalization, laboratory examination, liver zymogram and CRP test results (Table I). This study was approved by the Ethics Committee of Shanghai Ninth People’s Hospital. Signed written informed consents were obtained from the patients and/or guardians before the study.

**Methods.** All children received macrolide antibiotics and the clinical symptoms improved after treatment. The levels of anti-*M. pneumoniae* IgA, IgM, and IgG in serum were measured at different time points at early stages, during the development of pneumonia, and after pneumonia. The levels of anti-*M. pneumoniae* IgM and IgG in serum were measured by ELISA (Ben-Bio, San Diego, CA, USA). The levels of anti-*M. pneumoniae* IgA in serum were measured with the CHORUS kit according to the manufacturer’s instructions (Diese Diagnostica Senese, Siena, Italy). The positive cutoff values for anti-*M. pneumoniae* IgA, IgM and IgG were 18 AU/ml (the upper and lower limits were 10 and 100 AU/ml, respectively), 950 and 320 AU/ml, respectively.

### Results

*M. pneumoniae* IgM potency and pre-hospital fever duration. To investigate the correlation between *M. pneumoniae* IgM potency and pre-hospital fever duration, we divided the patients into three groups according to the duration of fever before admission: i) 0-3 days, ii) 4-6 days, and iii) 7-10 days. Most children (40%; 32/80) had <3 days of fever before admission; 27 patients (33.8%) had 4-6 days of pre-hospital fever; and 21 patients (26.3%) had 7-10 days of pre-hospital fever. The results showed that the potency of *M. pneumoniae* IgM, but not IgA or IgG, was positively correlated with pre-hospital fever duration (r=0.377, P=0.002) (Fig. 1).

### Table I. Clinical data and blood test results of neonates with mycoplasma-associated pneumonia.

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Mean ± standard error (range)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>16.6±5.3 (8-27)</td>
<td>0.859</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>31/49</td>
<td></td>
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<tr>
<td>Pre-hospital fever duration (days)</td>
<td>4.3±2.7 (0-10)</td>
<td>0.014</td>
</tr>
<tr>
<td>Total fever duration (days)</td>
<td>5.7±3.4 (0-15)</td>
<td>0.426</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>7.3±5.0 (2-14)</td>
<td>0.210</td>
</tr>
<tr>
<td>Red blood cells (million/µl)</td>
<td>4.6±0.4 (3.4-5.7)</td>
<td>0.526</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.6±1.0 (10.1-14.4)</td>
<td>0.855</td>
</tr>
<tr>
<td>Platelets (1,000/µl)</td>
<td>271.2±76.4 (114.0-454.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>White blood cells (1,000/µl)</td>
<td>9.2±3.9 (3.8-20.7)</td>
<td>0.158</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>26.3±11.3 (5.0-65.0)</td>
<td>0.465</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1.9±2.8 (0.0-8.6)</td>
<td>0.100</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.3±0.4 (0.0-3.0)</td>
<td>0.216</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>7.0±3.0 (1.8-14.0)</td>
<td>0.089</td>
</tr>
<tr>
<td>AST (µ/l)</td>
<td>34.6±11.3 (22.0-65.0)</td>
<td>0.634</td>
</tr>
<tr>
<td>ALT (µ/l)</td>
<td>20.2±13.2 (9.0-66.0)</td>
<td>0.603</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>43.5±42.6 (1.4-215.4)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

The P-value represents the correlation between the patient’s clinical data and the initial value of *M. pneumoniae* IgM. The duration of fever before admission and the platelet number were closely correlated with the *M. pneumoniae* IgM potency. *M. pneumoniae, Mycoplasma pneumoniae, IgM, M. pneumoniae immunoglobulin M.*
that of anti-\textit{M. pneumoniae} IgA in the diagnosis of neonatal mycoplasma-associated pneumonia.

\textbf{Discussion}

The course of mycoplasma infection is often relatively long. In adults, \textit{M. pneumoniae} can still exist one week after medical treatment (8). Our results showed that most newborns with mycoplasma-associated pneumonia were admitted to the hospital within one week (4.3±2.7 days) after \textit{M. pneumoniae} infection. The possible explanation is that fever is the main
clinical symptoms in children, but persistent cough is the typical symptom in adults. Compared with adults, newborns with infection can be admitted earlier to hospital. Our results showed that many children (21/80, 26.3%) were negative for \textit{M. pneumoniae}-specific antibodies at admission. To avoid false negatives, two serum samples were used to test \textit{M. pneumoniae} IgA, IgM and IgG after admission.

Previous studies reported that serum anti-\textit{M. pneumoniae} IgA is a good indicator for the detection of \textit{M. pneumoniae} infection in adults (10-12). Detection of serum \textit{M. pneumoniae} IgA in adults is more sensitive for the diagnosis of \textit{M. pneumoniae} infection than detection of IgM (8). However, this conclusion is inconsistent with the results reported by Yamazaki et al (9) who found that serum \textit{M. pneumoniae} IgA was a poor indicator of \textit{M. pneumoniae} infection. Here, we examined the efficacy of \textit{M. pneumoniae} IgA in the diagnosis of neonatal mycoplasma-associated pneumonia. The positive rates of serum \textit{M. pneumoniae} IgM and IgA were 63.8 and 33.8%, respectively, on the day of admission. These rates were positively correlated with the duration of fever before admission. We also found that the positive rate of serum \textit{M. pneumoniae} IgM was higher than that of IgA in all the groups classified by pre-hospitalization fever duration, suggesting that detection of serum \textit{M. pneumoniae} IgA is less sensitive than IgM in the diagnosis of neonatal mycoplasma-associated pneumonia. This may be explained by the immature immune system of newborns.

In our study, the positive rate of \textit{M. pneumoniae} IgM was 63.8% in patients with an average duration of 4.3±2.7 days before admission. This result is consistent with a previous report (13). That is, the positive rate of \textit{M. pneumoniae} IgM was 62.2% in the first week after mycoplasma infection and ranged from 70.9 to 81.8% in the second week after infection (14,15). The sensitivity of serological testing is limited by the specimen, the standard diagnostic method and the method of detection. This may be used to explain the high sensitivity of \textit{M. pneumoniae} IgM in patients with longer hospitalization. We found that the positive rate of \textit{M. pneumoniae} IgA was positively correlated with the pre-hospitalization fever duration, although this correlation was lower than the correlation between IgM and pre-hospitalization fever duration.

The 4-fold increase of \textit{M. pneumoniae} IgG in the acute phase and the reversion of the disease is considered the gold standard for diagnosis of \textit{M. pneumoniae} respiratory tract infection (16). Medjo et al (14) reported that 90% of the patients with 4-fold increase of \textit{M. pneumoniae} IgG antibody potency in two sera also showed throat swab \textit{M. pneumoniae} positive. However, 38.8% of patients in this study had a 4-fold increase in \textit{M. pneumoniae} IgG antibody potency in two sera. Thus, anti-\textit{M. pneumoniae} IgG cannot provide a timely diagnosis of \textit{M. pneumoniae} infection. Given the complications of obtaining two sera from newborns, \textit{M. pneumoniae} IgG is not the best indicator to diagnose \textit{M. pneumoniae} infection.

In conclusion, detection of \textit{M. pneumoniae} IgM has higher sensitivity in the diagnosis of neonatal mycoplasma-associated pneumonia than that of the detection of \textit{M. pneumoniae} IgA. Two sera detection can more effectively improve the diagnostic accuracy.

References


