Epidemiology of C. pneumoniae

The prevalence of approximately 50% has been found in adults worldwide with small regional differences (3). We also studied the antibody prevalence of C. pneumoniae in healthy persons and patients with acute respiratory infections (4).

The microplate immunofluorescence antibody (MFA) technique was used in measuring chlamydial antibodies in this study. In this test, patients with IgG titers of \( \geq 64 \) were considered to have had past infection. By this criteria, positive serum antibodies against C. pneumoniae were found in 67.4% of healthy persons and in 74.2% of adult patients with respiratory infections. High antibody titers of IgG \( \geq 512 \), or IgA \( \geq 128 \) against C. pneumoniae were demonstrated more frequently in patients than in healthy persons. The prevalence of antibody against C. pneumoniae was lower than 10% in children 5 years old or younger. The antibody prevalence increased rapidly between ages 6 and 15, reaching a plateau of 60%.

From these results, we estimated that in Japan a high infection rate might occur in children at nursery schools, kindergartens and elementary schools.

**Rate of C. pneumoniae respiratory infections**

In Western countries, C. pneumoniae infection is reported to constitute 4–12% of community acquired pneumonia and bronchitis and 1–9% of upper respiratory tract infections (3).

In our hospital during the last 3 years, C. pneumoniae was shown to cause 8.1% of the cases of pneumonia, 6.8% of acute upper respiratory tract infections and bronchitis. C. pneumoniae was found to be associated with 4.7% of exacerbation of chronic lung disease including chronic obstructive pulmonary diseases (COPD) (5). Therefore, C. pneumoniae should be considered as an important respiratory pathogen.

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**3. Current Topics of Chlamydial Respiratory Tract Infections — Special Reference to the Epidemiology and Clinical Findings of Chlamydia pneumoniae Infections in Japan**

Toshio Kishimoto and Rinzo Soejima

**Key words:** Chlamydia pneumoniae, respiratory tract infections, Chlamydia

**Introduction**

Among the respiratory infections caused by Chlamydia, Psittacosis due to Chlamydia psittaci is the most well-known disease. Recently, Chlamydia trachomatis pneumoniae in newborns and infants has been added. Most recently, a new agent Chlamydia pneumoniae has been shown to be a common cause of respiratory infection. Therefore, the epidemiology of chlamydial respiratory infections has been broadened by the recognition of new Chlamydia. Here, we would like to report the epidemiology and clinical findings on C. pneumoniae respiratory infections in Japan.

**Classification of Chlamydia**

The genus Chlamydia was originally separated into two species, i.e. C. psittaci and C. trachomatis. Later a third species called C. pneumoniae was established in 1989 by researchers in the University of Washington in Seattle (1). In 1992, the fourth species, called C. pecorum, was separated from C. psittaci by Fukushi and Hirai (2). This species includes agents from ruminants. The species C. pecorum is not known to infect humans. Therefore, only the first three species should be considered in differential diagnosis.

**Epidemiology of C. pneumoniae**

Epidemiological studies on C. pneumoniae have been conducted throughout the world. A high rate of antibody prevalence of approximately 50% has been found in adults worldwide with small regional differences (3). We also studied the antibody prevalence of C. pneumoniae in healthy persons and patients with acute respiratory infections (4).

The microplate immunofluorescence antibody (MFA) technique was used in measuring chlamydial antibodies in this study. In this test, patients with IgG titers of \( \geq 64 \) were considered to have had past infection. By this criteria, positive serum antibodies against C. pneumoniae were found in 67.4% of healthy persons and in 74.2% of adult patients with respiratory infections. High antibody titers of IgG \( \geq 512 \), or IgA \( \geq 128 \) against C. pneumoniae were demonstrated more frequently in patients than in healthy persons. The prevalence of antibody against C. pneumoniae was lower than 10% in children 5 years old or younger. The antibody prevalence increased rapidly between ages 6 and 15, reaching a plateau of 60%.

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Clinical findings of *C. pneumoniae* infections

There are several reports on the clinical findings of *C. pneumoniae* infections (3, 5). The findings reported here are based on 37 cases of acute *C. pneumoniae* infection diagnosed by serology and isolation (6) (Table 1).

These cases included 17 cases of pneumonia and 20 cases of other respiratory tract infections including one case of pleuritis. Pneumonias were seen more frequently in elderly while other respiratory tract infections including one case of pleuritis. Pneumonias were seen more frequently in elderly while other respiratory tract infections including one case of pleuritis.

Underlying respiratory diseases were found only in less than half of the patients. A great majority of these patients were COPD (asthma, chronic bronchitis, emphysema, diffuse panbronchiolitis).

Twenty-five (67.6%) cases had dry cough as the initial symptom. Eleven (40.0%) of the 25 cases had dry cough persisted for more than 4 weeks. Therefore, a prolonged dry cough may suggest *C. pneumoniae* infection. Most of the cases showed no fever or low grade fever while only 11 cases (29.7%) had fever over 38°C.

Laboratory data were not particular. There were 10 cases (27.0%) of leucocytosis (≥ 10,000/mm^3) and 9 cases (24.3%) of positive CRP (++ or greater). This points to a relatively mild inflammatory reaction in most cases. However, ESR was moderately high.

Chest X-ray of 17 pneumonia cases showed involvement of the middle and lower lungs. Seven cases revealed a fine localized infiltration and 9 cases, a dense homogeneous infiltration.

Table 1. Clinical Findings of *C. pneumoniae* Infections

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Other RTI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>10-49</td>
<td>3</td>
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</tr>
<tr>
<td>50-69</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>70-</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Underlying Resp. Dis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Initial Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry cough</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Fever (38°C)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sputum</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC ≥10,000</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>CRP ± +</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>CRP ± ++</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>ESR ≥50 mm/h</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Epidemics and outbreak of *C. pneumoniae* infections

Epidemics of *C. pneumoniae* infection have been reported (3). The seroepidemiological studies have shown that epidemics of *C. pneumoniae* infections occur in the Western countries in a 4 to 6 year cycle like *Mycoplasma pneumoniae* infection (3). During our four-year survey from 1988 to 1991, we were not able to observe an epidemic. However cases of high antibody titers were found at greater frequencies in the months of November to April. All of the 14 isolates obtained in our hospital were between December and March. The serological data also suggested infections were more common in winter and spring.

There also have been reports on outbreaks in households, schools, offices, etc (3, 7, 8). However, mode of transmission and length of incubation period have not been well documented.

Recently, we encountered an outbreak of *C. pneumoniae* infection. We were able to trace the source of infection to a family and spread of infection to the schools in which the children attended.

We are planning to present a more detailed report on this outbreak later. Therefore, we shall present only a brief description of this case here (Fig. 1).

The index case was a 28-year-old housewife from Okayama City who was seen at the Kawasaki Medical School Hospital on November 5, 1992, with complaints of dry cough which persisted for over one month. She was diagnosed as acute bronchitis. Because she had acute antibody titers against *C. pneumoniae*, *C. pneumoniae* infection was diagnosed. The family history revealed the 31-year-old husband and 4- and 3-year-old daughters also had respiratory symptoms. Therefore, the whole family was examined.

The husband and younger daughter were diagnosed to have acute bronchitis, and older daughter pneumonia. The whole family had acute antibody titers and *C. pneumoniae* was isolated from the throat of these 3 family members. This family moved from Okayama City to Kurashiki City on the 29th of November, 1992 to live with the mother’s brother, who had a son and his parents live with him. At the end of December the 6-year-old nephew and the 54-year-old father developed bronchitis and pharyngitis, respectively. *C. pneumoniae* was isolated from the throat of the boy and *C. pneumoniae* antigen was detected in the throat of the father by IDEIA and PCR. The family had spent...
one night together on a trip one week before they lived together. Otherwise there had been no contact before that time.

Based on this information, the incubation period of *C. pneumoniae* was estimated to be about 3–4 weeks. We further investigated whether the infection spread to the schools that the children attended.

The transmission was then traced to the nursery school and kindergarten which the children of the primary and secondary cases attended. The younger girl in the index family attended the S nursery school in Okayama City before she moved to Kurashiki City and her 6-year-old cousin was attending the D kindergarten in Kurashiki City.

A survey of the two schools was conducted on February 6 and 7, 1993, respectively.

Acute antibodies were found in 12 (14.0%) of 86 students at the S nursery school as well as 8 (17.0%) of 47 family members of the S nursery students.

At D kindergarten, 2 (7.7%) of 26 students were shown to have acute antibodies. However, acute antibodies were not detected in 23 family members tested. Chlamydial antigens were detected by IDEIA in 3.5% of students in S nursery school and in 11.5% of students in D kindergarten.

*C. pneumoniae* was isolated in 4 (4.7%) students in S nursery school and 2 (7.7%) students in D kindergarten.

A survey of another kindergarten in Kurashiki City was conducted to determine whether this outbreak is an epidemic. The test results were negative for antigen detection and isolation. The patients were treated with antichlamydial agents. We are planning to follow the outcome of therapy in the patients and their family members. The following points were learned from this study:

1) Transmission is a non-vector type, i.e. an air-borne or droplet transmission from man-to-man.
2) Incubation period is 3–4 weeks.
3) Transmission occurs only after repeated and close contact.
4) Small outbreaks may occur in households and schools where persons have prolonged close contact.
5) Unlike acute viral infections, *C. pneumoniae* spreads slowly. It takes 4–5 months to run its course even in small size schools of 60–200 students.

In conclusion, *C. pneumoniae* may cause small outbreaks of respiratory infection with illness similar to other viral infections. Therefore, *C. pneumoniae* should be considered in the differential diagnosis for acute respiratory infection.

**References**

4. Transfiguration of Rickettsial Diseases: Tsutsugamushi Disease and Spotted Fever Group Rickettsiosis in Japan

Yoshiki Tang and Yuzuru Kobayashi

Key words: Rickettsia infection, tsutsugamushi disease, spotted fever group rickettsiosis

1. Tsutsugamushi disease

Tsutsugamushi disease has been recognized for more than a hundred years in northern Honshu as a serious endemic disease. However, in 1948, it was established that another type of tsutsugamushi disease exists in Japan (1). This so-called new type of tsutsugamushi disease, transmitted by Leptotrombidium pallidum or L. scutellare, has been found in almost the entire country, and is epidemiologically, clinically different from the classical tsutsugamushi disease, transmitted by L. akamushi. Since 1975, the number of patients with this disease (mainly the new type) has increased in almost all parts of Japan, reaching about 800 in a year.

1) Serological classification of Rickettsia tsutsugamushi

It has been well known that strains of R. tsutsugamushi display a marked degree of antigenic heterogeneity. Three classic representative strains, the Gilliam, Karp and Kato, were established in 1962, and have been used for serological study. However, newly isolated strains have shown serological variety, and it was suggested that the antigenicities of these strains differ from those of the three classic strains.

For serological classification and antigenic analysis of R. tsutsugamushi, we produced monoclonal antibodies against the classic strains and the newly isolated ones. The serological reactivity of the anti-Gilliam, anti-Karp and anti-Kato monoclonal antibodies showed varied reactive characteristics, i.e., serotype-specific, species-specific and intermediate reactivities (2). The reactivity of these monoclonal antibodies against the newly isolated strains of Miyazaki, Niigata and Ehime Prefectures revealed that the strains of Ehime were identified as the Karp or Kato type (3), but the other strains were serologically different from the classic ones (4). Thus, we produced monoclonal antibodies against the Irie and Hirano strains isolated in Miyazaki, and the Shimokoshi strain in Niigata, and analyzed their reactivity (5). The strains of Miyazaki were classified into the Irie and the Hirano types, using the serotype-specific monoclonal antibodies. In contrast, the antigenicity of the Shimokoshi strain differed from those of the other strains. From these results, the strains of R. tsutsugamushi of Japan fell into six serotypes, the Gilliam, Karp, Kato, Irie, Hirano and Shimokoshi, using each serotype-specific monoclonal antibody (Table 1).

2) Laboratory diagnosis

The laboratory diagnosis is made either by isolation of R. tsutsugamushi from the blood of a patient or by demonstrating the specific antibody in convalescent serum using immunofluorescence or immunoperoxidase techniques. Recently, a polymerase chain reaction (PCR) method has been developed for determination of the diagnosis during the early acute stage. Furuya et al reported a PCR method to detect R. tsutsugamushi DNA from blood clots of patients (6). Murai et al reported a nested PCR method to detect it from peripheral blood mononuclear cell samples of patients (7). The PCR method will be useful for rapid and specific diagnosis of tsutsugamushi disease in the early acute stage.

2. Spotted fever group (SFG) rickettsiosis in Japan

SFG rickettsiosis is widely endemic throughout the world. In Japan, Mahara et al first reported the cases of SFG rickettsiosis which occurred in Anan City, Tokushima, in 1984 (8). Thereafter, patients were reported in Kochi, Miyazaki, Hyogo, Kagoshima, Shimane, Chiba, Mie Prefectures, and the number of patients reached about 100.

1) Characterization of the causative rickettsia

The causative rickettsia was first isolated by Uchida et al from a patient in Kochi in 1986 (9). We isolated the Katayama and Abe strains in Tokushima and the Misaka and Kojima strains in Hyogo from patients, between 1987 and 1990, and