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Mycoplasma pneumoniae and *Chlamydia pneumoniae* infections in children with pneumonia

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Mycoplasma pneumoniae *and* Chlamydia pneumoniae *infections in children with pneumonia. S. Esposito, F. Blasi, F. Bellini, L. Allegra, N. Principi, and the Mowgli Study Group. ©ERS Journals Ltd 2001.*

ABSTRACT: The most common clinical signs, host responses and radiographic patterns were studied in 203 Italian children hospitalized for community-acquired pneumonia in order to clarify the role of clinical and radiological characteristics in the diagnosis of *Mycoplasma pneumoniae* and/or *Chlamydia pneumoniae* infections.

Antibody measurements in paired sera and polymerase chain reaction on nasopharyngeal aspirates were used to establish the diagnoses of acute *M. pneumoniae* and *C. pneumoniae* infection, and the aetiologic data were correlated with the clinical, laboratory and radiographic data obtained on admission.

No significant association was observed between evidence of *M. pneumoniae* and/or *C. pneumoniae* infection and periods of episode during the year, mean age of the study subjects, individual symptoms, physical findings or laboratory test results. Furthermore, no significant correlation was observed in relation to the radiological findings and *M. pneumoniae* and/or *C. pneumoniae* infection.

This study shows that neither clinical findings nor laboratory parameters distinguished *Mycoplasma pneumoniae* and/or *Chlamydia pneumoniae* infection in children with pneumonia. Radiological findings also have a limited capacity to differentiate aetiologic agents. The priorities for future research include the development of rapid, easily accessible and cost-effective diagnostic tests useful for each episode of pneumonia in children.

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Recent studies reported that *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* play a significant role as causes of community-acquired pneumonia in children of all ages [1–3]. Since these atypical pathogens may cause chronic colonisation of the respiratory tract [4, 5] and are not susceptible to the β-lactam regularly used for the treatment of paediatric pneumonia [6, 7], rapid diagnostic tests are important. The designation of specific clinical and radiological features to an aetiologic agent has been common practice [8, 9], but recent data have cast doubt on the specificity of these observations when comparing individual clinical manifestations [10–13]. The diagnosis of *M. pneumoniae* and *C. pneumoniae* infections relies on serology, cultures and polymerase chain reactions (PCR), all of which are clinically impractical [14, 15]; it would therefore be beneficial if clinical characteristics, nonspecific inflammatory parameters and the type of infiltration in a chest radiograph could be used to identify these pathogens.

There are few data concerning the possibility of differentiating *M. pneumoniae* and *C. pneumoniae* infections on the basis of presenting manifestations in children with pneumonia. Therefore, the most common clinical signs, host responses and radiographic patterns in 203 Italian children hospitalized for community-acquired pneumonia were studied, in order to clarify further the clinical, biological and radiological characteristics of acute *M. pneumoniae* and/or *C. pneumoniae* infections. The most advanced set of microbiological methods were used to establish the diagnoses of *M. pneumoniae* and *C. pneumoniae* infection, and correlated the aetiologic data with the clinical, laboratory and radiographic data obtained on admission.

Materials and methods

Study subjects

The study involved 203 children aged 2–14 yrs, who were admitted to hospitals in 21 Italian municipalities between May 1998 and April 1999. The patients were hospitalized on the basis of the clinical decisions of the physicians on duty. Previously healthy male and female children aged 2–14 yrs, with signs, symptoms and chest radiographs consistent with community-acquired pneumonia, were considered eligible for inclusion. Exclusion criteria included severe concomitant diseases (neoplasia, kidney or liver disease, immunodepression, cardiovascular disease, malabsorption syndrome), nosocomial acquired infections and use of antibiotics in the 48 h before enrolment. The study protocol was approved by the Institutional Review Boards at each of

the centres and informed consent was obtained from the parents or legal guardians of each child before enrolment.

Methods

Upon admission, systematic recordings were made of the patients' medical history, rectal temperature, respiratory frequency and auscultation findings. This information was collected on a detailed data form, prepared in order to standardize the interpretation of clinical findings. Blood samples were taken for host response measurements: white blood cell (WBC) count, serum C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Total and differential WBC counts were determined using an automatic cell counter, serum CRP concentration was measured by means of immunonephelometric method and ESR using the Westergren method. Serum was collected for *M. pneumoniae* and *C. pneumoniae* antibody measurements: immunoglobulin (Ig)M and IgG to *M. pneumoniae* were tested by means of an enzyme-linked immunosorbent assay (Pantec, Turin, Italy), whereas IgM, IgG and IgA to *C. pneumoniae* were evaluated by means of microimmunofluorescence (Labsystems, Helsinki, Finland). Nasopharyngeal aspirates were also obtained, immediately immersed in sucrose-phosphate-glutamate transport medium, and stored at -70°C until assayed for the presence of *M. pneumoniae* and *C. pneumoniae* deoxyribonucleic acid (DNA). PCR for both pathogens was performed as previously described [16, 17]. Chest radiographs (erect posteroanterior and lateral view) were taken in the hospital of admission and were then centrally reviewed by an experienced radiologist who was naive to the patients' clinical history or laboratory data. Seven radiological features (hyperinflation, peribronchial wall thickening, perihilar linear opacities, reticulo-nodular infiltrate, segmental or lobar consolidation, bilateral consolidations and pleural effusion) were recorded as present or absent [18]. Radiographic interpretation alternatives were not mutually exclusive and in each radiogram, more than one category could be checked. Between four and six weeks after admission, repeat blood samples for *M. pneumoniae* and *C. pneumoniae* antibody measurements were taken during the convalescent evaluation.

Acute *M. pneumoniae* and/or *C. pneumoniae* infection was diagnosed if the patient had a significant antibody response to one of the pathogens in paired sera (IgM antibody, a 4-fold increase in IgG antibody titre, a static IgG antibody titre four times or more than the cut-off of the assay) or if the PCR on nasopharyngeal aspirates was positive for one of them [6].

Analysis

The data were analysed using SAS Windows v.12 (Cariy, NC, USA). All of the patients were included in the analysis. For all of the statistical tests, a p-value of <0.05 was considered statistically significant. Parametric data were compared using analysis of variance (ANOVA) with terms for treatment and tests for multiple comparisons. When the data were not normally distributed, or were non parametric data, the Kruskal-Wallace test was used. Categorical data were analysed using contingency table analysis and the Chi-squared or Fisher's test.

Results

Of the 203 enrolled children, 110 (54.2%) were males and 93 (45.8%) were females. The mean $\pm$ SD age of the study population was 5.44 ± 3.06 yrs: 96 (47.3%) children were aged 2–4 years, 58 (28.6%) 5–7 years, and 49 (24.1%) 8–14 years old. Sixty-eight children (33.5%) had evidence of acute *M. pneumoniae* infection confirmed by serology (18 patients), PCR (4: among them, two were aged 2–4 years and two aged 5–7 years), or both (46). There were eight (4%) children with acute *C. pneumoniae* infection: two identified by serology, three by PCR (among them, two were aged 2–4 years and one aged 5–7 years) and three by both. A further 11 patients had acute *M. pneumoniae* and *C. pneumoniae* coinfection, confirmed by serology (all with evidence of acute infection for both pathogens) and PCR (ten nasopharyngeal aspirates positive for *M. pneumoniae* DNA and five positive for *C. pneumoniae*). Table 1 shows the distribution of infections by months of the year. Even if minor variations were detected, no significant difference was observed for the different aetiological agents in various months of the year.

The clinical characteristics of the study population at enrolment are summarized in table 2. Age distribution was similar between the groups. Moreover, no significant association was observed between evidence of *M. pneumoniae* and/or *C. pneumoniae* infection and individual symptoms or physical findings. The clinical presentation (including disease onset, the presence of a similar illness in the family, cough, tachypnea, fever, rales and wheezes) was similar in the children with acute *M. pneumoniae* or *C. pneumoniae* infection and those with acute mixed *M. pneumoniae* and *C. pneumoniae* infection. Fever was the prevalent sign in all aetiological categories. The most common findings on physical examination were rales. The duration of illness and hospitalization was similar in the different groups of children: no significant differences were observed between subjects with acute *M. pneumoniae* or *C. pneumoniae* infection and those with acute mixed *M. pneumoniae* and *C. pneumoniae* infection.

Table 3 shows the laboratory data by aetiological groups. No significant difference was detected in total and differential WBC count, CRP or ESR in the children with acute *M. pneumoniae* or *C. pneumoniae* infection and those with acute mixed *M. pneumoniae* and *C. pneumoniae* infection. The distribution of WBC, CRP and ESR values was wide within each group.

The radiographic characteristics of the study population are shown in table 4. No significant correlation was observed in relation to the radiological findings considered as single or associated variables and *M. pneumoniae* and/or *C. pneumoniae* infection.

Table 1. – Distribution of infections by months of the year

Months	*Mycoplasma pneumoniae* infection, n = 68	*Chlamydia pneumoniae* infection, n = 8	Mixed *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infection, n = 11
May – July (n = 40)	16 (40.0)	1 (2.5)	2 (5.0)
August – October (n = 36)	10 (27.7)	2 (5.5)	1 (2.7)
November – January (n = 69)	22 (31.8)	1 (1.4)	5 (7.2)
February – April (n = 58)	20 (34.4)	4 (6.8)	3 (5.1)

Data are presented as number (percentage). No significant differences were observed.

Discussion

Distinguishing acute *M. pneumoniae* and *C. pneumoniae* infections may have some merit because they do not respond to β-lactam antibiotics [6, 7] and require specific antimicrobial therapy in order to avoid chronic infections with late sequelae [4, 5]. These pathogens have been commonly called atypical [19, 20] because, in some cases, the clinical presentations were different from those associated with pneumococcal infection [20]. However, most of the information pertaining to the clinical and radiological presentation of atypical bacterial pneumonia comes from adult case series and reports.

This is a large, prospective, multicentre study of paediatric pneumonia performed all around Italy during a one-year study period. Considering that the incidence of infections remained almost stable during different months of the year, the findings do not seem to be related to a clear local outbreak caused by *M. pneumoniae* or *C. pneumoniae*.

The present results are in line with previous data casting doubt on the sensitivity and specificity of clinical and laboratory features in predicting the aetiology of community-acquired pneumonia in children [21 – 23]. None of the clinical characteristics or laboratory parameters considered by us seem to be unique to atypical bacterial infections, which suggests that they are not useful for therapeutic decision making. It was not possible to predict these aetiological agents only on the basis of the presenting manifestations. WBC, CRP and ESR (all commonly used to measure the severity of the acute phase response) are nonspecific parameters that may be affected by a number of physical, chemical or microbial stimuli [24, 25]. Moreover, in mucosa-limited infections (typical of most community-acquired pneumonia episodes in developed countries) WBC, CRP and ESR values tend to remain low [26]. Their potential for differentiating aetiological agents is therefore highly limited, and considerable overlapping of individual values has been reported in aetiological groups [10, 11].

Radiological diagnosis is subject to the same problems of clinical efficacy as other diagnostic medical tests. The radiographic diagnosis of pneumonia is made on the basis of pulmonary perihilar opacities or infiltrates (airways disease) and/or consolidation (air-space disease) [18, 27]. Like other screening tests, radiological findings are limited in terms of sensitivity, specificity and intra- or inter-observer variability. In the population studied, no feature characterised *M. pneumoniae* and/or *C. pneumoniae* infection and the radiograph cannot be used to predict atypical bacteria infection precisely. These observations are particularly important because, although their appropriateness may be debatable, many clinicians base their decisions regarding the initiation of antibiotics on chest radiographs [28].

Four children positive for *M. pneumoniae* DNA and three positive for *C. pneumoniae* DNA were considered infected although there was no serologic evidence of acute infection. These children might also be considered simply carriers. However, the number of patients with a significant increase in specific *M. pneumoniae* antibodies was so high that these four children do not affect the conclusions of the study. On the other hand, it is well known that the lack of an immunological response after *C. pneumoniae* infection may be caused by an immature

Table 2. – Clinical characteristics of the study population at enrollment

Characteristics	*Mycoplasma pneumoniae* infection, n = 68	*Chlamydia pneumoniae* infection, n = 8	Mixed *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infection, n = 11
Mean age, yrs	6.32 ± 3.34	5.76 ± 2.94	6.90 ± 3.36
Onset			
Gradual	41 (60.3)	6 (75.0)	6 (54.5)
Acute	27 (39.7)	2 (25.0)	5 (45.5)
Similar illness within the family	4 (5.8)	1 (12.5)	1 (9.0)
Cough	44 (64.7)	4 (50.0)	7 (63.6)
Tachypnea	8 (11.7)	0	1 (9.0)
Fever	58 (85.2)	5 (62.5)	10 (90.9)
Rales	60 (88.2)	7 (87.5)	10 (90.9)
Wheezes	10 (14.7)	1 (12.5)	1 (9.0)
Days of illness	13.17 ± 6.67	10.75 ± 4.27	13.00 ± 5.50
Days of hospitalization	6.51 ± 2.74	6.38 ± 2.88	6.33 ± 3.39

Data are presented as means ± SD or number (percentage). No significant differences were observed.

Table 3. – Laboratory data in the various aetiological groups.

Parameter	*Mycoplasma pneumoniae* infection, n = 68	*Chlamydia pneumoniae* infection, n = 8	Mixed *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infection, n = 11
WBC, cells·μL^{-1}	13564 ± 8836	14035 ± 10173	8074 ± 2117
Neutrophils, %	66 ± 17	67 ± 14	59 ± 8
Lymphocytes, %	24 ± 15	23 ± 13	31 ± 9
Monocytes, %	7 ± 5	8 ± 4	8 ± 3
Eosinophils, %	2 ± 2	1 ± 1	2 ± 2
Basophils, %	0.4 ± 0.6	0.7 ± 0.7	0.3 ± 0.3
CRP, μg·dL^{-1}	53 ± 83	58 ± 70	18 ± 16
ESR, mm·h^{-1}	49 ± 33	49 ± 25	41 ± 15

Data are presented as mean values ± SD; WBC: white blood cell count; CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. No significant differences were observed.

Table 4. – Comparisons of radiographic characteristics of the study population.

Finding	*Mycoplasma pneumoniae* infection, % (n = 68)	*Chlamydia pneumoniae* infection, % (n = 8)	Mixed *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infection, % (n = 11)
Hyperinflation	10 (14.7)	2 (25.0)	2 (18.2)
Peribronchial wall thickening	3 (4.4)	2 (25.0)	2 (18.2)
Perihilar linear opacities	41 (60.3)	4 (50.0)	8 (72.7)
Reticulo-nodular infiltrate	27 (39.7)	1 (12.5)	5 (45.5)
Segmental or lobar consolidation	19 (27.9)	3 (37.5)	2 (18.2)
Bilateral consolidations	5 (7.4)	0	0
Pleural effusion	4 (5.9)	0	0

No significant differences were observed.

ability to produce a specific humoral response or poor antigenic stimulation in children [29]. Earlier prospective studies in paediatric patients with respiratory infections suggest that over 50% of subjects infected with *C. pneumoniae* fail to develop antibodies, and most of these patients are under 5 years of age [29 – 31]. Interestingly, also two out of the three children with PCR positive for *C. pneumoniae* DNA and no serologic evidence of acute infection were younger than 5 years of age.

Moreover, 11 children showed mixed acute *M. pneumoniae* and *C. pneumoniae* infection. Mixed infections are common in children with respiratory syndromes but their clinical implications are not clear [32]. In a recent study, HEISKANEN-KOSMA *et al.* [33] showed that mixed chlamydial-mycoplasmal infections constituted 20% of *M. pneumoniae* infections and as many as 35% of *C. pneumoniae* infections. The important unanswered question in this regard is whether one pathogen simply facilitates the penetration of the other pathogen, or whether both truly cause pneumonia. Moreover, it is not known if the combination of *M. pneumoniae* and *C. pneumoniae* lead to a more severe clinical illness.

In conclusion, this study shows that, although they are commonly used to do so, neither clinical findings nor laboratory parameters such as white blood cell count, serum C-reactive protein and erythrocyte sedimentation rate were informative for distinction of *M. pneumoniae* and/or *C. pneumoniae* infection in children with pneumonia. Radiological findings also have a limited capacity to differentiate these pathogens. The priorities for future research include the development of rapid, easily accessible and cost-effective diagnostic tests useful for each episode of pneumonia in children.

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