Chlamydial pneumonia in Costa Rica: results of a case-control study

J. M. Farrow¹ & J. B. Mahony²

This paper presents a brief review of chlamydial pneumonia in infancy and indirect evidence that the incidence of this disease may be high in developing countries. The results of a case-control study in Costa Rica, involving 39 cases of pneumonia and 43 controls (cases of diarrhoea), suggest that chlamydial pneumonia is of considerable public health importance there. Thirteen out of the 39 (33%) cases of pneumonia had serum antibody to Chlamydia trachomatis serovars D, E, F, G and L2, whereas only 1 out of the 43 controls was IgM-antibody positive (P<0.001). The occurrence of chlamydial pneumonia as a major health problem in developing countries is discussed.

That Chlamydia trachomatis causes pneumonia among neonates was first suggested by Schachter et al. in 1975 (1). Beem & Saxon (2) subsequently described the distinctive clinical presentation of chlamydial pneumonia which is characterized by tachypnoea and "staccato" cough⁶ without fever or significant malaise. The chest X-ray typically shows hyperexpansion with diffuse interstitial and patchy alveolar infiltrates. The patients, all under six months of age, demonstrate elevated serum IgG and IgM and often a mild eosinophilia. In the absence of appropriate antibiotic treatment, the course is protracted, with cough and tachypnoea requiring weeks to clear and radiographic changes persisting for a month or more. Although originally thought to be a benign disease, more recent research suggests that long-term sequelae of chlamydial pneumonia may be common (3).

It has since been shown in a number of studies that the infection is contracted by the neonate during passage through the birth canal of an infected mother. The prevalence of infection with chlamydia in pregnant women has been found to range from 2% to 25% and the risk of developing a chlamydial infection in an infant delivered vaginally to a mother with an infected cervix has been shown to be 60-70% (4). Of the exposed infants, 25-50% will develop conjunctivitis in the two weeks following delivery, and 10-20% will develop pneumonia in the first three to four months of life (4).

Although growing numbers of reports of chlamydial pneumonia are received from the industrialized world, little is known regarding the prevalence of this infection in developing countries. However, a high prevalence of C. trachomatis genital infection (5-9) and presumed transmission to infants with chlamydial ophthalmia neonatorum (10, 11) in developing countries have been documented.

In view of the link between chlamydial sexually transmitted disease (STD) and chlamydial pneumonia in industrialized countries, and given the high prevalence of chlamydial STDs and evidence of chlamydial ophthalmia neonatorum in the developing world, it is likely that chlamydial pneumonia would be a frequent occurrence in developing countries. The primary objective of this study was therefore to investigate the association between chlamydial infection and infant pneumonia in a less developed country, and to establish what proportion of cases of infant pneumonia may be attributable to chlamydia.

MATERIALS AND METHODS

A hospital-based, prospective case-control study was conducted from 1 April to 30 June 1985, at the
Hospital Nacional de Ninos in San Jose, Costa Rica. As a tertiary care hospital of the Costa Rican Department of Social Security, it is the main paediatric referral hospital for the country.

**Pneumonia cases and controls**

Cases in this study were restricted to infants between the ages of two weeks and six months from greater San Jose, who had been admitted to the hospital with radiologically confirmed pneumonia. All such cases were included in the study. These patients were from the lower and middle classes. To eliminate inter-observer variability, all the X-rays were read by a single radiologist.

The control group consisted of 43 consecutive cases of diarrhoea from the same geographical area and in the same age and socioeconomic group who had been admitted to the same hospital during the study period.

**Serology**

Following confirmation of the diagnosis, approximately 0.5 ml of blood was obtained by fingerprick using appropriate equipment. Serum was separated from clot by centrifugation and then frozen and stored at −40 °C. The frozen sera were transported to St. Joseph’s Hospital in Hamilton, Ontario, where testing was performed blind. *C. trachomatis* IgM and IgG antibodies were measured by solid-phase immunoassay (EIA), as described by Mahony et al. (12). Serum dilutions of 1:800 and 1:200 were selected as the thresholds of positivity for IgM and IgG antibody, respectively. Microimmunofluorescence (MIF) assay for *C. trachomatis* IgM and IgG antibody was performed, as described (12), using prototype serovars which were obtained from Dr J. Schachter, University of California, San Francisco.

**RESULTS**

Thirty-nine infants with pneumonia under the age of 6 months (cases) and 43 controls with diarrhoea were studied for serological evidence of *C. trachomatis* infection. The age, sex, length and weight of cases and controls were comparable, as shown in Table 1.

Serological evidence of recent *C. trachomatis* infection (IgM >1:800; serovars D, E, F, G and L2) was obtained in 13 of the infants with pneumonia and in only one of the controls; this difference between cases and controls was significant (*P* <0.001).

Of the 82 patients in the case and control groups, only 49 returned for follow-up testing. Only 6 infants were seropositive for IgG antibodies to *C. trachomatis* by either EIA or MIF. Serovar analysis revealed IgG antibodies to serovars D, E, F, G and L2. In only two of these was there a fourfold increase observed in chlamydia IgG antibody titres between acute and convalescent specimens. Both infants were in the chlamydial pneumonia group and both also had chlamydial IgM antibody.

To approximate the relative risk of pneumonia among infants with *C. trachomatis* infection, the odds ratio was calculated and found to be 21 (confidence interval by Woolf’s method, 2.6 to 170.1).

No significant differences in temperature, pulse or respiratory rate were found between those patients who were seropositive to *C. trachomatis* and those who were seronegative. We observed a difference in the proportion of infants with elevated eosinophil counts between the seropositive infants with pneumonia (5/9, 56%) and seronegative pneumonia cases (4/23, 17%), which approaches the level of significance (*P* =0.05). There was no significant difference with respect to eosinophil counts between those infants in the seronegative pneumonia group and those infants with diarrhoea (3/25, 12%).

All 13 infants with pneumonia who had chlamydial IgM antibody showed a similar X-ray pattern of mixed interstitial and alveolar infiltrates, while no consistent pattern was seen in those who were seronegative.

**DISCUSSION**

The results of this case–control study confirm that infection by *C. trachomatis* is a risk factor for pneumonia among infants in Costa Rica. Thirteen infants out of 39 presenting with pneumonia were identified with chlamydial IgM antibody as measured by EIA and MIF. Serovar analysis by the MIF test indicated IgM antibody to serovars D, E, F, G and L2. The sera were treated to remove chlamydial IgG antibody and rheumatoid factor to eliminate IgM false-positive EIA results, but the possibility of polyclonal B-cell stimulation cannot be ruled out. The latter is unlikely.

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<th>Table 1. Comparison of data on cases and controls</th>
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however, owing to the very low prevalence of chlamydial IgG antibody in our cases and controls. The presence of C. trachomatis IgM antibodies to serovars D, E, F, G and L2 rules out TWAR strains of C. psittaci as the cause of pneumonia in our cases.

The strong association between chlamydial IgM antibody and pneumonia suggests a causal link. However, the relative risk, estimated here by the odds ratio, gives little idea of the public health significance of exposure to this risk factor. The proportion of pneumonia attributable to chlamydial infection in this age group (under 6 months) has been estimated indirectly from our case-control study, using Levin's formula (13), to be nearly 32%. Such a derivation of the attributable risk for the population is valid only to the extent that the prevalence of the disease is low, and if the proportion of controls exposed is similar to the proportion of the general population exposed to the risk factor. Although hospital-based control groups are often not representative of the general population, the observed proportion of controls with serological evidence of systemic infection with C. trachomatis (1/43 or 2.3%) is similar to that noted in the North American study described above (4). In any case, this study provides suggestive evidence that chlamydial pneumonia and other systemic chlamydial infections have public health significance in this age group and deserve further epidemiological investigation.

Further studies will also be required to assess the nutritional, seasonal and geographical (e.g., urban vs rural) risk factors for chlamydial pneumonia. Other aspects of the natural history of chlamydial infections, such as chronic pulmonary sequelae and the association of perinatal genital chlamydial infection with low birth weight and premature rupture of membranes, also deserve further investigation.

Beem & Saxon's description of chlamydial pneumonia was that of a disease characterized by cough, tachypnoea, normal temperature, and eosinophilia with an X-ray pattern of diffuse interstitial and patchy alveolar infiltrates (2). Our cases showed the characteristic radiologic appearance and most of them presented with eosinophilia, but there was no significant difference between chlamydial and non-chlamydial pneumonia in terms of temperature or respiratory rate. The lack of definitive criteria to differentiate between chlamydial and non-chlamydial pneumonia in the context of primary health care points to the need for a simple diagnostic test for use in the field, or for a standard treatment regimen for pneumonias in patients under 6 months of age that would be effective against C. trachomatis.

A link between sexually transmitted C. trachomatis and pneumonia in infants has been established in the developed world. The high prevalence of chlamydial sexually transmitted disease in the developing countries suggests that chlamydial pneumonia may be a significant public health problem there as well. Our study provides direct evidence that C. trachomatis pneumonia due to serovars D, E, F, G and L2 occurs in the developing world. However, global generalizations are not yet warranted as Costa Rica shares features with the more industrialized countries. Further investigations in other developing countries are needed.

ACKNOWLEDGEMENTS

This study was supported by a grant from the International Development Research Centre, Ottawa, Canada. Laboratory facilities and valuable technical assistance were provided by the Instituto de Investigaciones en Salud, University of Costa Rica.

The help of many people who assisted in conceiving, planning and conducting this study and in commenting on drafts of this report is gratefully acknowledged. They include Dr. F. Chavarria, Dr. Max Chernesky, Dr. Robert Douglas, Ms Patricia Hart, Dr. Michael Hills, Dr. Rosa Jimenez, Dr. Leonardo Mata, Dr. Richard Mathias, Dr. Edgar Mohs, Dr. Laura Rodrigues, Dr. Peter Smith, Dr. Sally Stansfield and Dr. John Treharne.

RÉSUMÉ

PNEUMOPATHIE À CHLAMYDIA AU COSTA RICA: RÉSULTATS D'UNE ÉTUDE CAS–TÉMOINS

La pneumopathie à chlamydia a été identifiée pour la première fois en tant que maladie par Beem et Saxon en 1977. Depuis lors, il est apparu que l'agent étiologique de cette affection, Chlamydia trachomatis, est à l'origine de nombreuses pneumopathies du nourrisson dans les pays développés. La littérature actuelle fait état de très peu de renseignements concernant l'importance des pneumopathies à chlamydia dans les pays en développement. Comme le
nouveau-né contracte cette affection à la naissance pendant son passage dans la filière génitale, et comme les affections à chlamydia transmises par voie sexuelle sont courantes dans les pays en développement, les pneumopathies à chlamydia y sont aussi probablement assez communes.

Cette étude cas– témoins, qui a été menée à San José, au Costa Rica, établit la comparaison entre la séropositivité pour les IgM anti-Chlamydia trachomatis chez un groupe de nourrissons âgés de 2 semaines à 6 mois et celle observée dans un groupe témoin de nourrissons de même âge admis dans le même hôpital avec un diagnostic de diarrhée. Sur les 39 nourrissons admis pour pneumopathie, 13 présentaient des anticorps dirigés contre Chlamydia trachomatis sérovars D, E, F, G et L2. Sur les 43 enfants atteints de diarrhée, un seul était séropositif. On a trouvé dans ce cas un risque relatif de 21 et l'analyse statistique a établi que l'infection générale due à Chlamydia trachomatis constitue un des facteurs de risque de pneumopathie dans cette population. L'intensité de l'association laisse en fait à penser qu'il y a relation de cause à effet.

A partir de cette étude, on a estimé qu'environ 32% des pneumopathies retrouvées dans cette classe d'âge de cette population sont attribuables à une infection par Chlamydia trachomatis.

REFERENCES