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Chlamydia trachomatis: a major agent of respiratory infections in infants from low-income families

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Abstract

Objectives: To determine the prevalence of lower respiratory tract infection (LRTI) due to *Chlamydia trachomatis* in newborn infants and to describe the clinical, laboratory, and radiological characteristics of the disease.

Methods: A cross-sectional study carried out over a 12-month period. All infants up to 6 months of age admitted consecutively at the Centro Pediátrico Professor Hosannah de Oliveira of the Universidade Federal da Bahia in Salvador, Brazil, and diagnosed with LRTI according to clinical and/or radiological criteria were included in the study. *C. trachomatis* infection was diagnosed by the enzyme-linked immunosorbent assay (ELISA) for the detection of IgM-class antibodies. The prevalence of LRTI by *C. trachomatis* was determined and the prevalence ratios for the infection and clinical or laboratory variables were calculated.

Results: One hundred and fifty-one infants were submitted to serology for *C. trachomatis* and 15 (9.9%) tested positive. Chlamydial infection was found only in infants under 5 months of age, mainly in those aged under 2 months. Three of the infants with *C. trachomatis* infection were born by cesarean section. Conjunctivitis and eosinophilia had occurred in 33.3% of the cases. Chest X rays were abnormal in 92.0% of cases. There was an association between *C. trachomatis* infection and the duration of hospitalization exceeding 15 days ($p = 0.0398$) and oxygen therapy ($p = 0.0484$).

Conclusions: There was a high prevalence of *C. trachomatis* respiratory infection in the population studied. The infection was associated with a more severe form of the disease, emphasizing the importance of testing pregnant women for this infection to avoid infection in the newborn infant.

J Pediatr (Rio J). 2012;88(5):423-9: Chlamydia trachomatis, respiratory tract infection, pneumonia, bronchiolitis, infant.

Introduction

According to the World Health Organization (WHO), 92 million cases of *Chlamydia trachomatis* infection occur in adults annually worldwide, 9.5 million in Latin America and the Caribbean.[1] It is the most prevalent sexually transmitted disease in the United States (2.8 million cases/year).[2] In Brazil, data on the prevalence of infection by this agent in adults are based on isolated studies conducted in specific populations, with reported prevalence rates ranging from 2.1 to 25.7%[3-5] depending on the study population and the diagnostic methods used.

In adults, *C. trachomatis* causes genital infections that are usually asymptomatic; however, it is a significant

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cause of inclusion conjunctivitis and respiratory infections in newborns[6] as well as lower respiratory tract infection (LRTI) in the first 6 months of life.[7-16] Around 10-20% of children of infected mothers develop pneumonia,[6,17] with significant medical and social repercussions that would be preventable with good prenatal care.

Few studies have been conducted in Brazil on the role of *C. trachomatis* in the etiology of LRTI in newborn infants.[11,18] The objective of this study was to determine the prevalence of LRTI due to *C. trachomatis* in infants admitted to a university teaching hospital in Salvador, Brazil, and to describe the clinical, laboratory, and radiological characteristics of the disease in these patients.

Methods

This cross-sectional, observational study was conducted between April 2006 and March 2007 at the Centro Pediátrico Professor Hosannah de Oliveira (CPPHO), a pediatric center of the Universidade Federal da Bahia (UFBA), Salvador, Brazil.

Study population

All infants up to 6 months of age admitted consecutively to the hospital and diagnosed with LRTI or pneumonia or bronchiolitis, according to clinical and/or radiological criteria, were included in the study. Infants with severe comorbidities unrelated to LRTI were excluded.

Diagnostic procedures and data collection

The following tests were performed: full blood count, erythrocyte sedimentation rate, C-reactive protein, serological studies, detection of respiratory viral infections by indirect immunofluorescence for respiratory syncytial virus, adenovirus, influenza A and B viruses, and parainfluenza 1, 2 and 3 viruses, and polymerase chain reaction (PCR) for bocavirus and rhinovirus. *C. trachomatis* infection was diagnosed by enzyme-linked immunosorbent assay (ELISA) for the detection of IgM-class antibodies, using commercial kits (NovaTec®, Dietzenbach, Germany), strictly in accordance with the manufacturer's instructions. The test was considered positive when the optical density of the evaluated serum was above the cut-off value determined for each plate. Blood cultures were performed whenever clinically indicated.

The infants were submitted to posteroanterior and lateral chest X rays. Two pediatric radiologists, blinded to the patient's clinical history, independently evaluated the radiographies. When the two radiology reports failed to agree, the X rays were further evaluated by a third pediatric radiologist. The final radiology report was issued based on agreement between two of the three evaluators.

The following variables were evaluated: gender, age, gestational age at birth, breastfeeding, type of delivery, mother's age, mother's education level, prenatal care, family income, maternal vaginal discharge, history of conjunctivitis, history of fever, duration of symptomatology at the time of admission to hospital, symptoms at admission, fever during hospitalization, diagnosis of pneumonia, diagnosis of bronchiolitis, radiological signs, use of oxygen, co-infection by cytomegalovirus, leukocyte count, eosinophil count, and duration of hospitalization.

Pneumonia was defined as the presence of coughing and/or difficulty in breathing, associated with radiological changes.[19] Bronchiolitis was defined as the occurrence of tachypnea (≥ 50 breaths per minute) and/or dyspnea and/or diffuse wheezing, associated or not with radiological changes of hyperinflation and/or atelectasis.

Statistical analysis

The prevalence of LRTI by *C. trachomatis* was determined, and the prevalence ratios for the infection were calculated in accordance with the variables evaluated, which were selected to permit comparison with associations previously described in the literature and/or to evaluate the severity of the infection. Findings were considered statistically significant when the probability of a type I error was < 5% ($p < 0.05$).

Ethics approval

This study was approved by the Internal Review Board of the Maternidade Climério de Oliveira, UFBA, under protocol number 23/2004.

Results

Characteristics of the study population

Overall, 168 infants of 0-6 months of age were admitted to the CPPHO with LRTI, and 157 were included in the study; the remaining 11 being excluded based on the exclusion criteria. Ninety-five participants (60.5%) were male and their mean age was 87.0±52.2 days (range 10-210 days; median 71 days). Mean age of the mothers was 23.8±6.1 years (range 14-41 years; median 23 years). Median family income was minimum wage. The principal complaints that led parents to seek the healthcare service were: coughing (94.3%), nasal obstruction (84.7%), and breathing difficulties (75.2%).

Prevalence of C. trachomatis *infection*

One hundred and fifty-one infants (96.2%) were submitted to serology for *C. trachomatis* and 15 of these (9.9%) tested positive. One or more viruses were detected in 62% of the 134 samples evaluated for respiratory viruses (Figure 1).

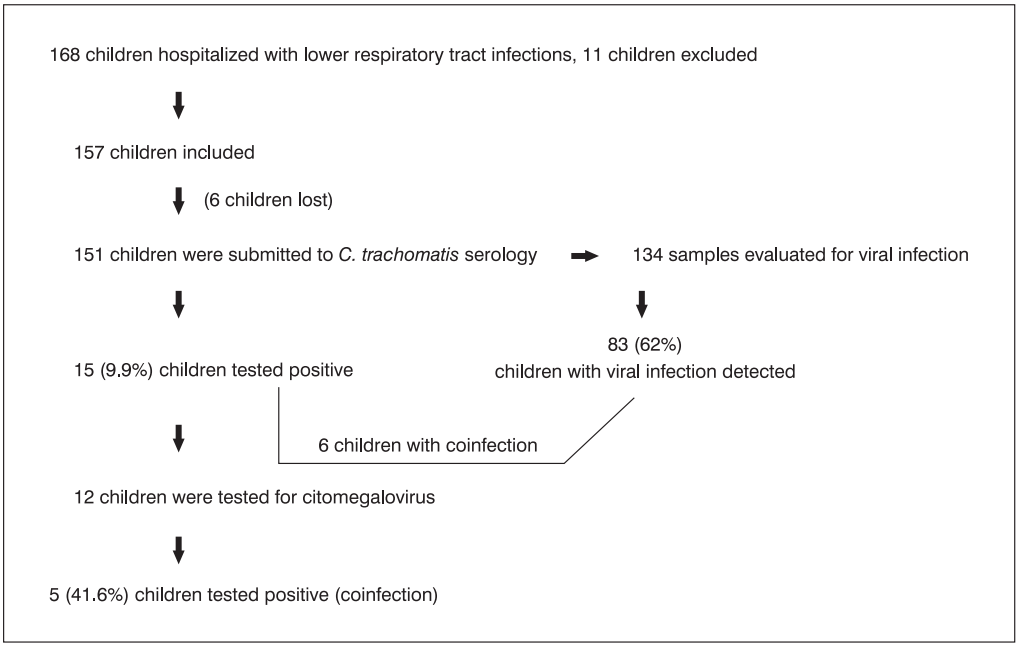

Figure 1 - Summary study results

Six infants with *C. trachomatis* infection were co-infected with a respiratory virus: three cases of respiratory syncytial virus and one case each of influenza B, parainfluenza virus 3 and rhinovirus.

Twelve infants with *C. trachomatis* infection were tested for cytomegalovirus, with five (41.7%) testing positive.

Demographic, clinical and laboratory characteristics of C. trachomatis *respiratory infection cases*

Of the 15 cases of *C. trachomatis* infection that were detected, eight were in boys (53.3%). Mean age of the infants was 63.5±28.9 days (range 35-117 days; median 52 days). Mean maternal age was 22.2±4.6 years (range 18-37 years). Fourteen mothers (93.3%) had attended prenatal care and six had had a vaginal discharge during pregnancy, five in the final trimester. Twelve infants were born vaginally and three by cesarean section. Six mothers had premature rupture of membranes. Of the three *C. trachomatis*-positive infants born by caesarean section, two had mothers who developed premature rupture of membranes. Five infants had a history of conjunctivitis, three within the first 8 days of life. Of those with *C. trachomatis* infection, only one infant was premature and had a low birth weight. Thirteen infants were being breastfed, nine exclusively.

All infants had a cough, nasal obstruction and breathing difficulties. There was a history of fever in five cases (33.3%), and 12 patients (80.0%) had a runny nose. The mean interval between the onset of the respiratory symptoms and admission to hospital was 12.9±10.8 days (range 2-37 days; median 9 days). Blood cultures were performed on 11 infants; however, only one patient tested positive for a nosocomial *Klebsiella pneumoniae* infection.

Ten infants with *C. trachomatis* infection were diagnosed with pneumonia at admission to hospital, while the remaining five were diagnosed with bronchiolitis. Wheezing was detected in 11 babies (73.3%), four of whom had a viral co-infection. Crepitations were detected in 13 infants (86.7%). Mean leukocyte count in this group was 14,033±6,662 cells/mm^3, and mean eosinophil count was 484±864 cells/mm^3.

Only three patients had fever ≥ 37.8 ºC while hospitalized. The mean duration of hospitalization was 12.9±4.1 days (range 5-18 days). During hospitalization, 11 patients (73.3%) required oxygen therapy, and all received antibiotic therapy consisting of erythromycin in 13 cases (86.7%). Of these, 12 patients improved and were discharged from hospital, while one tested positive for a nosocomial *Klebsiella pneumoniae* infection and was transferred to the intensive care unit (ICU). Of the two children who were not submitted

to treatment with erythromycin, one was discharged in good clinical condition, and the other developed respiratory failure and was transferred to the ICU.

Radiological findings

All 15 infants were submitted to chest X rays. Twelve cases were evaluated by two radiologists, and one case was considered normal. The remaining three cases were not evaluated by the study radiologists; however, pediatricians described consolidation in two cases, while the other case was considered normal. Hyperinflation and interstitial infiltrate were the principal findings (Table 1). One child had a radiological diagnosis of pleural effusion associated with hyperinflation and interstitial infiltrate. This finding suggests a bacterial co-infection; however, blood culture was negative in this case.

Table 1 - Radiological findings (n and %) in lower respiratory chlamydial infection in infants

Radiological findings	n	%
Atelectasis	1	8.4
Pleural effusion	1	8.4
Hyperinflation	7	58.4
Interstitial infiltrate	8	66.7
Pneumonia	1	8.4
None	1	8.4

Association between C. trachomatis *infection and the variables studied*

An association was found between *C. trachomatis* infection and the following variables: symptomatology > 7 days, symptomatology > 15 days, no fever, oxygen therapy, co-infection by cytomegalovirus, and duration of hospitalization > 15 days (Table 2). To conduct a more thorough investigation into the possible effect of a viral co-infection on the associations found, prevalence ratios were calculated after excluding the infants with *C. trachomatis* and viral co-infections. In this subgroup, only the associations between *C. trachomatis* infection and oxygen therapy (p = 0.0484) or duration of hospitalization > 15 days (p = 0.0398) remained statistically significant.

Discussion

The prevalence of *C. trachomatis* respiratory infection of 9.9% found in this study is in agreement with data published in the literature reporting rates that range from 7.0% to around 30.0% in the first 6 months of life.[7-16,20]

Ejzenberg et al.[11] reported a prevalence of 10.3% of positivity for *C. trachomatis* in infants < 6 months of age admitted to a hospital in São Paulo, Brazil with LRTI. Other investigators have described higher prevalence rates of this infection in this age group.[7-10] Differences in prevalence rates between studies may be due to the population evaluated, which may have included cases of mild or severe respiratory disease. Infected children may be asymtomatic.[12] Symptomatic cases can vary in severity: only around 30% of infected infants develop pneumonia,[21] and only 20% of infected infants require hospitalization.[22] This study determined the prevalence of *C. trachomatis* infection in hospitalized infants with a more severe form of the disease.

A study conducted in Salvador, Brazil, in children under 5 years of age, admitted to hospital because of pneumonia, found a prevalence of *C. trachomatis* infection of 4.0%.[23] The lower prevalence found in that study may be due to the age group evaluated, which included older children in whom the occurrence of *C. trachomatis* infection is uncommon. Likewise, Pientong et al.[24] also investigated this bacteria in nasopharyngeal secretions by PCR and restriction fragment length polymorphism in Thai children of 1 month to 2 years of age and hospitalized with acute bronchiolitis. The prevalence of *C. trachomatis* infection was 2.4%, and occurred mainly in infants under 6 months of age. The selected population (children under 2 years of age diagnosed with bronchiolitis) may have contributed to the low prevalence observed.

Nasopharyngeal secretion cultures remain the gold standard for the diagnosis of *C. trachomatis* respiratory infection.[15,17,21] Nevertheless, technical difficulties prevent their routine use in clinical practice. More recently, nucleic acid amplification tests have begun to take the place of culture[17] due to the high sensitivity and specificity of these techniques.[25] Notwithstanding, none of these techniques has the approval of the U. S. Food and Drug Administration for use in nasopharyngeal specimens from infants.[17] There are several antigen-based detection methods such as direct fluorescent monoclonal antibody staining and enzyme immunoassays for the detection of *C. trachomatis*. However, the sensitivity of these tests with nasopharyngeal specimens ranges from 33 to 90%.[21] In this study, direct detection of C*. trachomatis* IgM was used for diagnosis – sensitivity with this test being estimated at 75 to 89%[15,16] and specificity at 88%.[16]

Some factors associated with a greater risk of *C. trachomatis* respiratory infection, such as having an adolescent mother and poor socioeconomic level, were investigated in this study; however, no association was found between these variables and the infection. Nonetheless, some limitations in the evaluation of socioeconomic level must be considered, since the study population consisted almost entirely of infants born into families with limited financial resources.

Table 2 - Prevalence ratio of *Chlamydia trachomatis* respiratory infection together with 95% confidence intervals and demographic, clinical and laboratory variables

Variables	n	Prevalence of chlamydial infection	Prevalence ratio	95%CI	p
Male	92	8.7%	0.73	0.28-1.94	0.54
Female	59	11.9%			
Prematurity					
Yes	32	3.1%	0.27	0.04-1.58	0.17
No	119	11.8%			
Age of the infant (months)					
< 2	68	14.7%	2.45	0.88-6.8	0.08
≥ 2	83	6.0%			
Breastfeeding					
Yes	104	12.5			
No	47	4.3	2.9	0.74-11.64	0.76
Maternal age < 20 years old*	36	5.6%	0.48	0.12-1.91	0.32
Maternal age ≥ 20 years old*	113	11.5%			
Mother's education level*					
Finished elementary school	67	4.5%	0.30	0.09-1.0	0.05
Some high school education	81	14.8%			
Family income*					
≤ one minimum wage	86	11.6%	1.59	0.47-5.35	0.48
> one minimum wage	41	7.3%			
Prenatal care*					
No	21	4.8%	0.44	0.07-2.59	0.41
Yes	128	10.9%			
Type of delivery*					
Vaginal or forceps	114	10.5%	1.61	0.49-5.32	0.64
Cesarean	46	6.5%			
Maternal vaginal discharge*					
Yes	48	12.5	1.36	0.51-3.6	0.53
No	98	9.2			
Previous conjunctivitis*	28	17.9%	2.14	0.77-5.99	0.55
No previous conjunctivitis	120	8.3%			
Duration of symptomatology					
> 15 days	14	28.6%	3.56	1.2-10.58	0.02
≤ 15 days	137	8.0%			
> 7 days	41	19.5%	3.07	1.16-8.13	0.023
≤ 7 days	110	6.4%			
Oxygen therapy*					
Yes	68	16.2%	3.34	1.13-9.98	0.028
No	82	4.9%			
Fever before hospitalization					
No	62	16.1%	2.92	1.04-8.08	0.03
Yes	90	5.5%			
Cytomegalovirus infection†					
Yes	9	55.6%	6.32	2.54-15.9	< 0.001
No	80	8.8%			
Leukocyte count*					
≤ 10,000	104	11.5%	1.64	0.5-5.45	0.43
> 10,000	43	7.0%			
Eosinophil count*					
> 300	24	20.8%	2.33	0.85-6.42	0.10
≤ 300	123	8.9%			
Duration of hospitalization					
≥ 15 days	29	20.7%	2.8	1.04-7.56	0.04
< 15 days	122	7.4%			

95%CI = 95% confidence intervals.
* Up to 15.9% of the data were missing.
† Only 89 infants were tested for cytomegalovirus.

The results of the present study call particular attention to the fact that *C. trachomatis* infection was found only in infants < 5 months of age, principally in those < 2 months of age, a group representing 75.0% of cases. The greater occurrence of this infection in infants of 2-3 months of age is in agreement with the findings of other studies.[12,13,20,26,27] Therefore, when there is a clinical suspicion of this infection, the fact that the infant is < 2-3 months of age should increase the etiological suspicion of *C. trachomatis* respiratory infection.

In contrast to some reports in the literature that the occurrence of *C. trachomatis* respiratory infection is rare in infants delivered by cesarean section,[21] 20.0% of the infants in the present study with this diagnosis were delivered by this route. This event has already been described, and the authors suggest that the infection may be transmitted following membrane rupture or in the uterus and not exclusively during the baby's passage through the birth canal.[16,28,29]

The reported association between chlamydial respiratory infection and conjunctivitis in 50.0% of cases[26] was lower in the present study in which only 33.3% of the infants had conjunctivitis, a finding that is in agreement with other reports in the literature.[13] Approximately 70% of infants with this respiratory bacterial infection failed to develop fever, thus confirming the classic description of the condition, afebrile pneumonia. The presence of eosinophilia > 300 cells/mm^3 is a common finding in *C. trachomatis* respiratory infections.[21] Nevertheless, in the present study, this abnormality was found in only five infants (33.3%). These results are in agreement with the study conducted by Carballal et al.[27] in Argentinean children.

The results of the present study show an association between *C. trachomatis* infection and symptomatology for > 15 days prior to hospitalization, duration of hospitalization > 15 days, the use of oxygen therapy, and co-infection by cytomegalovirus. The slow progression of *C. trachomatis* infection has already been reported in the literature.[6,26] In the evaluation performed on the subgroup of infants with this bacterial infection and no co-infection, only the associations with oxygen therapy and a longer period of hospitalization remained statistically significant. Rours et al.[20] conducted a retrospective evaluation of *C. trachomatis* infection using PCR in a sample of Dutch infants and also reported the occurrence of more severe forms of the disease in positive cases; however, this may be because the sample population in that study consisted almost entirely of infants with underlying diseases, unlike the sample in the present study.

Chest X rays were abnormal in 92.0% of the infants enrolled in the present study, which is well above the rate found in infants with a viral infection. A greater number of radiological findings together with a longer duration of hospitalization and the use of oxygen therapy suggest that *C. trachomatis* affects the lower respiratory tract more severely than respiratory viruses.

Some investigators have reported a strong association between *C. trachomatis* and other microorganisms,[8] cytomegalovirus being the most common co-infection.[8,9,26] The present results confirm this association, which has also been reported in a previous study.[30] Nevertheless, following exclusion of the group of infants co-infected with respiratory viruses, the association between *C. trachomatis* infection and cytomegalovirus no longer remained statistically significant. The low prevalence of *C. trachomatis* infection in infants with no other viral co-infections and the small number of patients investigated for cytomegalovirus may have hampered this analysis. Cytomegalovirus infection is associated with precarious socioeconomic conditions and other factors – such as adolescent motherhood and promiscuity,[8] conditions that are also associated with *C. trachomatis* infection, possibly contributing to the elevated occurrence of co-infection between these microorganisms.

Some limitations of the present study include the selection of the study population. Therefore, the data obtained do not refer to infants with milder respiratory infections who did not require hospitalization and who represent the majority of cases. Furthermore, the use of a single diagnostic method may have underestimated the prevalence of *C. trachomatis* infection. On the other hand, concurrent data collection and the inclusion of a large number of infants who were submitted to clinical, laboratory, and radiological evaluation including interpretation of the X rays by two or three specialist radiologists allowed the clinical and laboratory profile of the study population to be defined.

In conclusion, the prevalence of *C. trachomatis* infection in young infants admitted to a hospital for respiratory infections in Salvador, Brazil, was high, and this infection was associated with a more severe form of the disease. This emphasizes the importance of testing pregnant women for this infection in order to avoid transmission of the infection to the newborn infant. In addition, it is important to consider this etiologic agent when evaluating infants with a respiratory infection.

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