

Case report

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***Chlamydia trachomatis* infection in early neonatal period**

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Abstract

Background: The clinical characteristics of *Chlamydia trachomatis* respiratory tract infections in Japanese neonates were investigated.

Methods: Clinical, laboratory and microbiological characteristics of five infants with pneumonia due to *C. trachomatis* in early neonatal period were analyzed.

Results: Only *C. trachomatis* was identified in 4 infants. Both *C. trachomatis* and cytomegalovirus was identified in one. Wheezing, tachypnea and cyanosis were common in infants. Mothers of five infants had negative chlamydial EIAs at 20 weeks of gestation.

Conclusions: We identified five cases of *C. trachomatis* respiratory tract infections in early neonatal period with the possibility of intrauterine infection. Targeted screening, early diagnosis, and effective treatment of perinatal and neonatal chlamydial infections seems to be necessary

Background

Chlamydia trachomatis has been recognized as a pathogen of nongonococcal urethritis, salpingitis, endocervicitis, pelvic inflammatory disease, inclusion conjunctivitis of neonates, follicular conjunctivitis of adults, infantile pneumonia and associated diseases. [1] Genital or respiratory tract chlamydial infections still have been recognized as a major public health problem throughout the world including Japan.

Pneumonia due to *C. trachomatis* is a disease limited for the most part to infants less than 6 months of age. It has been suggested that *C. trachomatis* infection in pregnant women may be related to premature labor and to perinatal complications. Although transmission of the organism from mothers to their infants generally occurs at the time of delivery with passage of the infant through the infected endocervix, the possibility of intrauterine infection at late pregnancy has been reported.[2,3] Gencay and colleagues

[4] studied *C. trachomatis* infection in mothers with pre-term delivery and intrauterine transmission of the infection to their offspring. Their results strongly suggest that mothers and their preterm babies may benefit from screening for active *C. trachomatis* infection.

Reported below, are the cases of *C. trachomatis* respiratory tract infections in early neonatal period with the possibility of intrauterine infection. Clinical characteristics of *C. trachomatis* respiratory tract infections in Japanese neonates were investigated.

Methods

Patients

Annually 150 to 200 neonates were admitted to the neonatal intensive care unit (NICU) of the Hokkaido Children's Hospital and Medical Center, Otaru, Hokkaido, Japan. Each year we screened 30 to 50 neonates who had respiratory tract symptoms for chlamydial infections. Five

neonates with *C. trachomatis* infection were admitted to NICU during the time of January 1995 to December 2001. Case 1 was a female born by vaginal delivery after 39 week's gestation with a birth weight 2605 g; Case 2 was also female born after 40 week's gestation by Caesarean section because of fetal distress with a birth weight of 3025 g. No asphyxia was found at birth and was no episode of premature rupture of membrane (PROM) in both cases. Tachypnea or cyanosis developed days 3 and 13 in Case 1 and 2 respectively. Case 3 was a male born by vaginal delivery after 37 week's gestation with a birth weight of 2982 g; Case 4 was a female born after 33 week's gestation also by vaginal delivery with a birth weight of 3025 g. There was an episode of meconium-stained amniotic fluid with Case 3. Chorioamnionitis was found in the placenta of Case 4. Wheeze and tachypnea developed within one day after delivery in Case 4. Case 5 was a male born after 37 week's gestation also by vaginal delivery with a birth weight of 3,714 g. Tachypnea and cyanosis developed from day 1 in Case 5.

For all patients oxygen saturation was measured initially and subsequently. Oxygen was administered when the arterial hemoglobin oxygen saturation was <90% with the use of nasopharyngeal catheters or nasal cannulas. Anaerobic cultures were included using unvented commercial blood culture bottles and incubating a blood agar subculture under anaerobic conditions.

Five infants were admitted with an initial diagnosis of pneumonia and associated complications. Chest radiographs of Cases 1, 2, 3 and 4 on admission showed streaky shadows and reticulogranular infiltrates over whole lung without hyperinflation. That of Case 5 on admission showed streaky shadow over the whole lung without hyperinflation. Blood examination of Cases 1 and 2 revealed increased C-reactive protein (13.1 and 6.5 mg/dl) and hyperleukocytosis (18,700 and 31,200/ μ l) without eosinophilia.

Blood examination of Cases 3 and 4 revealed normal or slight increased C-reactive protein (0.10 and 0.00 mg/dl) and hyperleukocytosis (38500/ μ l) in Case 4. Bacterial cultures from throat, urine, blood, feces and cerebrospinal fluid are all negative. Human cytomegalovirus (CMV) was isolated from urine of Case 5. Serum IgG and IgM antibodies against CMV were detected from maternal and infantile sera. Other viruses such as respiratory syncytial (RS) virus, influenza virus and enteroviruses were not identified from clinical specimens obtained from these 5 infants. Blood examination revealed increased C-reactive protein (2.90 mg/dl) and hyperleukocytosis (20, 800/ μ l) without eosinophilia.

Microbiological Methods

Both nasopharyngeal and conjunctival swabs were collected from 5 infants within 2 weeks after birth for antigen detection and the polymerase chain reaction (PCR) study. Endocervical swabs of mothers during pregnancy were also obtained. The PCR assay to amplify *Omp 1* gene and restriction fragment length polymorphism (RFLP) analysis were used to detect and distinguish serotypes from genotypes of *C. trachomatis* as reported previously.[5,6] At the first step, 1.4 kbp DNA fragment that is larger than a full length of the *Omp 1* gene was amplified. At the second step for nested PCR, 1.2 kbp DNA fragment, a full length of *Omp 1* gene was amplified. Genotyping was performed by *Hinf* I, *Hind* III and *Hha* I restriction analysis of amplified *Omp 1*.

A commercially available EIA test kit was also used to detect genus-specific chlamydial antigens. [7,8] Maternal serum, infantile serum and cord blood samples were obtained for standard microimmunofluorescence (MIF) assay to detect IgG and IgM antibodies against *C. trachomatis*. [2]

Results

For all of the infants, one or more infectious agent was identified. In 4 infants, only *C. trachomatis* was identified. Both *C. trachomatis* and CMV was identified in Case 5. All nasopharyngeal specimens tested for *C. trachomatis* by PCR or EIA were positive. Diagnosis of *C. trachomatis* respiratory tract infections was made by antigen detection or PCR assay in nasopharyngeal swabs and by the presence of specific serum IgM antibodies by MIF. Of the 5 infants diagnosed with chlamydial infection, 3 had elevated serum IgM titers and specific IgM antibodies against *C. trachomatis* in cord blood.

The serovars that we identified from nasopharyngeal swabs of these infants by PCR-RFLP were E and H. *C. trachomatis* was identified by PCR or EIA in conjunctival swabs obtained from 3 infants. The serovars we identified from conjunctival swabs were identical with those obtained from nasopharyngeal swabs. There was no association between carriage of *C. trachomatis* in respiratory tract and any other bacteremias.

After review of all the chest radiographs by the radiologists, 5 infants were considered to have radiologic pneumonia. There were more female. Clinical, laboratory and microbiological findings of five cases were summarized in Table 1. Wheezing, tachypnea and cyanosis were more common in patients with pneumonia, and apnea or retraction was not common. *C. trachomatis* was associated with reduced SaO₂.

Table 1: Clinical, laboratory and microbiological findings of five cases

Case	1	2	3	4	5
Sex	F	F	M	F	F
Gestational age (weeks)	39	40	37	33	37
Birth weight (g)	2,605	3,025	2,982	2,265	3,714
Mode of delivery	Vaginal	Caesarean	Vaginal	Vaginal	Vaginal
Apgar score at 1 min after birth	9	8	7	8	7
Age at onset (days after birth)	3	13	1	0	1
Symptoms at onset	Tachypnea	Cyanosis	Wheeze	Tachypnea	Tachypnea
Nasopharyngeal chlamydial antigen	+	+	+	+	+
Nasopharyngeal chlamydial DNA	+	+	+	+	+
Conjunctival chlamydial DNA	+	-	+	+	-
Identified serovar of <i>C. trachomatis</i>	E	E	E	E	H
Specific serum IgM antibodies					
Cord blood	1:128	<1:16	<1:16	1:32	1:32
21 days after birth	1:64	1:32	1:32	1:16	<1:16

Table 2: Maternal microbiological findings during pregnancy

Mother of Case	1	2	3	4	5
Premature rupture of membranes	no	no	no	no	no
Findings of placenta	unknown	unknown	unknown	Chorioamnionitis	normal
Presence of endocervical chlamydial antigen by EIA	no	no	no	no	no
Presence of bacterial or viral vaginosis	unknown	unknown	unknown	unknown	yes
Serum antibodies to <i>C. trachomatis</i> (20 week's gestation)					
IgG	1:256	not tested	not tested	1:256	1:256
IgM	<1:16	not tested	not tested	1:64	<1:16

Before admission none of the patients were receiving oral or intravenous antibiotics. Treatment with ampicillin and amikacin was initiated without success. Respiratory tract symptoms and radiological appearance improved gradually after oral erythromycin (40 mg/kg/per day) or clarithromycin (15 mg/kg/per day) administration for total of 14 to 28 days respectively. We also obtained the results of laboratory and microbiological examinations of mothers of five infants with *C. trachomatis* infection. Antenatal records were available for 5 infants, whose mothers were screened for *C. trachomatis* by EIA test only at 20 weeks of gestation. These mothers had negative chlamydial EIAs (Table 2). None of the mothers received oral or intravenous antibiotics administration during pregnancy.

Discussion

Maternal *C. trachomatis* infections during pregnancy may cause a variety of perinatal and neonatal complications. Epidemiological data suggested an association between colonization of the genital tract by *C. trachomatis* and an increased risk of preterm PROM.[9–11] *C. trachomatis* may

lead to abortion through excessive maternal immunogenic reaction to its heat shock protein 60 antigen. [12]

We evaluated the significance of detection of serum antibodies to *C. trachomatis* by ELISA at different time of pregnancy for early diagnosis of perinatal complications. [13] The incidence of perinatal complications was significantly higher in IgG and IgA antibodies-positive pregnant women at 30 weeks of gestational age. This fact also may indicate of maternal acquisition of re- or new chlamydial infection in later part of pregnancy. Intrauterine *C. trachomatis* infections acquired near the time of labor was considered to be associated with perinatal complications.

During the last decade there has been increased interest in possible pathogenic role of organisms that colonize the airways of preterm infants and cause disease processes that could be devastating in this age group.[14] *C. trachomatis*[1,15,16] has been studied in the context of the development of bronchopulmonary dysplasia (BPD.) While serological evidence has associated *C. trachomatis* with BPD, cultures for *C. trachomatis* have failed to confirm

these data. [16,17] Additionally, *C. trachomatis*, *Mycoplasma hominis*, and CMV have been implicated as etiologic agents for the development of BPD, [1,15-17] which was not supported by other findings.[14]

The serovars of *C. trachomatis* that we identified from Japanese infants and pregnant women were similar to those reported in other studies from non-trachoma-endemic areas of developed countries and were thought to be mainly urogenital tract-origin. [5,6] Similar results were also obtained from the study of adult inclusion conjunctivitis in Japan. [18] Antigenic variations of *C. trachomatis* were found among the strains from nasopharyngeal, conjunctival and endocervical origins.

Erythromycin and clarithromycin were thought to be not toxic for fetuses and effective for the treatment of endocervical infection of *C. trachomatis*. Some serological variants of *C. trachomatis* may have different pathogenicity or drug-sensitivity from classic serotypes. Early diagnosis and appropriate treatment of chlamydial infections may reduce perinatal complications. Oral administration of erythromycin or clarithromycin for the treatment of *C. trachomatis* respiratory tract infection in early neonatal period was also considered to be effective.

Antigen detection of *C. trachomatis* from the endocervix by EIA has been utilized widely for the purpose of the screening of chlamydial infections during pregnancy. However, chlamydial antigen was not detected by EIA from any endocervical specimens of mothers at 20 weeks of gestation. These tests are easily performed and less costly but have lower sensitivities than culture or PCR and have low positive predictive values in low prevalence populations such as Japan.[19]

Time of onset of respiratory tract symptoms of five infants in the present study was within 2 weeks after birth. One infant was born by cesarean section. Diagnosis of neonatal chlamydial infections was obtained by antigen or DNA detection from nasopharyngeal swabs and by detection of serum IgG and IgM antibodies to *C. trachomatis*. [2,3]

Our results as well as other investigators [4] demonstrate the clinical characteristics of *C. trachomatis* respiratory tract infections among infants in early neonatal period. Although the patients tested positive for *C. trachomatis* may not always have been associated with obvious symptoms, it has major role in perinatal mortality.[20] Control programs emphasizing targeted screening, early diagnosis, and effective treatment will have led to an eventual decline in the incidence of perinatal and neonatal chlamydial infections. [21] Approaches to prevention and treatment of chlamydial infections in pregnant women and infants seem to be necessary, including new antimi-

crobial interventions and the development of a vaccine strategy.

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