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Neonatal haemorrhagic conjunctivitis: a specific sign of chlamydial infection

新生兒出血性結膜炎：衣原體感染的特有病徵

Objective. To review the bacteriological causes and clinical features of acute neonatal conjunctivitis in a local paediatric centre.
Design. Retrospective review.
Setting. Paediatric unit of a regional hospital, Hong Kong.
Patients. All neonates who presented to Tuen Mun Hospital from 1 January 1996 to 31 December 2002 with persistent eye discharge and a positive eye swab culture.
Main outcome measures. Clinical features of neonates with chlamydial and non-chlamydial conjunctivitis.
Results. Of 90 neonates with positive eye swab or conjunctival scraping cultures, *Chlamydia trachomatis* was the second most common (n=19, 21%) cause of acute neonatal conjunctivitis after *Staphylococcus aureus* (n=32, 36%). All of the neonates with chlamydial conjunctivitis were delivered vaginally: two of them had concomitant chlamydial pneumonia. *Neisseria gonorrhoeae* conjunctivitis was rare (n=1, 1%). None of the mothers of neonates with *Chlamydia* had any history of sexually transmitted disease. The timing of presentation, gestational age, birth weight, and sex of the neonates did not suggest a risk of chlamydial infection. Nonetheless haemorrhagic eye discharge had a specificity of 100% and positive predictive value of 100% for chlamydial infection. There were no adverse ophthalmological consequences or complications of pyloric stenosis in any neonate following treatment with oral erythromycin.
Conclusions. Haemorrhagic eye discharge is a highly specific sign of neonatal chlamydial conjunctivitis. Early and prompt treatment with oral erythromycin is safe and effective.

目的：回顧本地兒科部有關患有急性結膜炎的新生兒的病原分析和臨床表現。
設計：回顧研究。
安排：地區醫院兒科部，香港。
患者：1996 年 1 月 1 日至 2002 年 12 月 31 日期間入住屯門醫院，眼部持續出現分泌物和拭子培養物呈陽性的新生兒。
主要結果測量：衣原體及非衣原體結膜炎的臨床表現。
結果：在 90 個帶有陽性眼部拭子或結膜脫離培養物的新生兒中，除金黃色葡萄球菌外（32 人，佔 36%），沙眼衣原體（19 人，佔 21%）是急性結膜炎的最常見病因。所有新生兒都是經陰道出生，其中兩個更同時患上衣原體肺炎。淋球菌性結膜炎則較為罕見（1 人，佔 1%）。所有急性衣原體結膜炎的新生兒的母親均沒有患過性病的病歷。根據新生兒的發病時間、妊娠週數、體重及性別，並沒有發覺任何導致衣原體感染的危險因素。不過，研究發現在診斷衣原體感染上，出血性眼分泌的病徵有 100% 特異性及 100% 陽性預計值。在所有完成口服紅黴素療程的嬰兒中，並沒有發現任何與眼睛有關的後遺症或幽門狹窄的併發症。
結論：出血性眼分泌是新生兒患有急性衣原體結膜炎的特有病徵。及早使用口服紅黴素是安全及有效的治療方法。

Key words:
Chlamydia infections;
Conjunctivitis, acute hemorrhagic;
Conjunctivitis, inclusion;
Infant, newborn

關鍵詞：
衣原體感染；
結膜炎，急性出血；
結膜炎，包涵體性；
嬰兒，新生的

Hong Kong Med J 2006;12:27-32

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Introduction

Neonatal conjunctivitis (ophthalmia neonatorum) is defined as inflammation of the conjunctiva which presents during the first month of life.[1] The causes can be septic (bacterial or viral) or aseptic (eg a chemical agent such as topical silver nitrate). Most cases of bacterial and viral conjunctivitis are self-limiting except

Chlamydia trachomatis and *Neisseria gonorrhoeae* that can result in blindness if left untreated.[2]

The increased take-up of high-quality antenatal care in the West and the use of intrapartum antibiotics to treat a positive high-vaginal swab have led to a dramatic reduction in the incidence of gonococcal conjunctivitis.[3,4] Chlamydial infection is nevertheless difficult to identify as it does not grow on routine culture medium. In addition, there is no reliable prophylactic topical agent. Topical eye drops such as silver nitrate effectively prevent gonococcal neonatal conjunctivitis but not chlamydial conjunctivitis.[5] It is important to eradicate the micro-organism from both the nasopharynx and the ophthalmic area to prevent recurrence.[6] *Chlamydia trachomatis* is now the most frequent identifiable infectious cause of neonatal conjunctivitis in the United States[7] and is a major worldwide health problem. The exact cause of neonatal conjunctivitis cannot generally be identified on clinical grounds alone. The timing of symptom onset[8] and a history of maternal sexually transmitted disease[9] (STD) may give some clues to the underlying cause but are definitely not diagnostic. Early diagnosis and prompt antibiotic treatment of chlamydial conjunctivitis are important if ocular complications are to be minimised,[10] but these remain a challenge for physicians. The clinical characteristics of neonates who had conjunctivitis in our hospital were collated in an attempt to determine the risk factors that may in turn predict the occurrence of chlamydial conjunctivitis.

Patients and methods

The clinical records of all neonates with bacterial conjunctivitis diagnosed by positive eye swab cultures or conjunctival scrapings from 1 January 1996 to 31 December 2002 in Tuen Mun Hospital were reviewed. Cases of clinical conjunctivitis with negative microbiological findings were excluded.

Since the early 1990s, routine practice has determined that all neonates who present with eye discharge undergo a thorough physical examination and full microbiological investigation that includes culture and microscopy for bacteria and *C trachomatis*. A detailed history is also recorded. A Gram stain is usually performed if a direct smear is received. The conjunctival scraping is usually inoculated at the bedside onto a chocolate agar plate for detection of bacteria and a Sabouraud dextrose agar plate for fungal detection. The chocolate agar plate is incubated at 37°C in the presence of 5% CO_2, and the Sabouraud dextrose agar plate at 37°C in ambient air. Direct antigen detection for *C trachomatis* by immunofluorescence testing using monoclonal antibody is performed if slides are prepared at the bedside. Chlamydial culture is performed for a specimen received in chlamydia transport medium. The shell vial culture method is used. The specimen in chlamydia transport medium is inoculated into a monolayer of McCoy cell line on a circular coverslip in a plastic vial and centrifuged at 35°C to 37°C for 1 hour and then incubated at 37°C in chlamydia growth medium in the presence of 2.5% CO_2. After 2 days of incubation, the inoculated cell monolayer is stained with commercially available conjugated monoclonal antibody against *C trachomatis* to look for the presence of immunofluorescence. If signs and symptoms of systemic upset are present, other investigations including nasopharyngeal aspirate, complete blood picture, blood culture, and chest X-ray are performed.

Broad-spectrum antibiotic eye drops, eg chloramphenicol or gentamicin, are prescribed empirically to those with eye discharge to eradicate common causative organisms (eg *Staphylococcus aureus, Escherichia coli*), while microbiological culture results are awaited. Systemic antibiotics (intravenous penicillin combined with an aminoglycoside) are prescribed if there is systemic upset. The final antibiotic regimen is dictated by discharge culture and bacterial sensitivity results. Neonates were identified as a definite case of chlamydial conjunctivitis only if *C trachomatis* was isolated in cell cultures.

Variables entered into the analysis included maturity, sex, growth parameters, clinical features such as presence of periorbital oedema, blood-stained eye discharge and systemic upset, and presence of parental history or symptoms of STDs. Treatment given and progress at follow-up were also noted.

The clinical features and demographic features of neonates with chlamydial and non-chlamydial conjunctivitis were compared using univariate analysis. A P value of less than 0.05 was considered significant. This part of statistical analysis was performed with the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], US). All organisms yielded were tabulated in decreasing frequency. CATmaker software (Centre for Evidence-based Medicine, Oxford, UK) was used to calculate the sensitivity, specificity, and positive and negative predictive values for different clinical characteristics.

Results

A total of 105 positive eye swab or conjunctival scraping cultures were identified from 90 neonates. Among these, 19 neonates were diagnosed to have chlamydial conjunctivitis with positive culture results while other bacteria caused the remaining 71 cases.

All neonates with chlamydial conjunctivitis were born at full-term except one (Table 1). All were delivered vaginally and were of an appropriate size for gestational age (growth parameters between 10th and 90th centiles). There were more females than males (58% vs 42%). All chlamydia-infected neonates had purulent eye discharge as the first symptom and the median age at presentation was day 7 of life (range, day 1-18). The purulent eye discharge was blood-stained in six (32%) cases (Fig). Periorbital oedema

Table 1. Chlamydial and other bacterial conjunctivitis

Characteristic	Chlamydial infection, n=19	Non-chlamydial infection, n=71	P value	Odds ratio (95% CI)
Maturity (weeks of gestations)				
Full-term	18	53	0.157	-
Preterm (range)	1 (36)	18 (31-36)		
Sex				
Female	11	27	0.119	-
Male	8	44		
Growth parameters (centile)				
>90th	0	2	0.459	-
50th-90th	11	32		
10th-50th	8	37		
<10th	0	0		
Mean No. of days of symptom onset (range)	7.42 (1-18)	7.35 (1-28)	0.334	-
Presence of blood-stained discharge				
Positive	6	0	<0.001	NC*
Negative	13	71		
Presence of periorbital oedema				
Positive	16	13	<0.001	0.28 (0.06-0.137)
Negative	2	58		
Not documented	1	0		
Presence of systemic upset				
Positive	4	23	0.338	-
Negative	15	48		
Parental history/symptoms of STD†				
Positive	0	7	0.159	-
Negative	19	64		

* NC non-calculable
† STD sexually transmitted disease

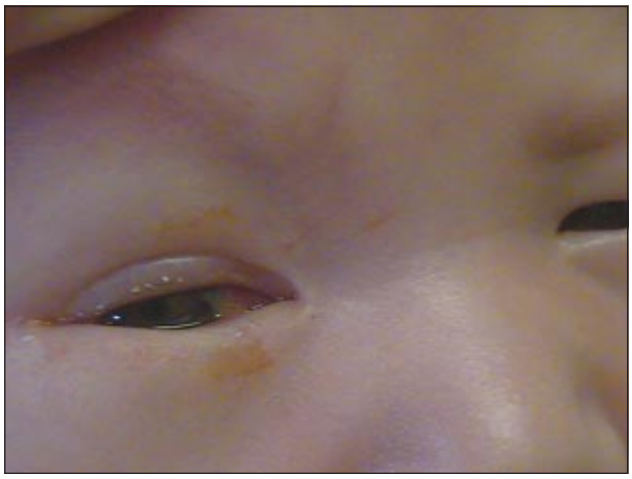

Fig. Haemorrhagic eye discharge in a neonate with culture-proven chlamydial conjunctivitis

was also a commonly observed clinical finding (84%). All parents denied a history or symptoms of STD. Two neonates had concomitant chlamydial pneumonia with consolidation shown on chest X-ray, and required intravenous antibiotics. All neonates with chlamydial conjunctivitis were prescribed systemic erythromycin (orally, 50 mg/kg per day in four divided doses for 14 days). Blood-stained discharge subsided within 2 days of commencing treatment.

Among the 71 cases of non-chlamydial conjunctivitis, *S aureus* (36%) and *E coli* (17%) were the two most common pathogens (Table 2). One quarter (25%) of these neonates were born prematurely (range, 31-36 weeks) and there was male predominance (62%). There was only one (1%) case of *N gonorrhoeae* conjunctivitis. The median age of presentation was day 7 of life (range, day 1-28), similar to the chlamydial group. No neonates had blood-stained eye discharge, although 13 (18%) had periorbital oedema. All the 71 neonates were prescribed topical chloramphenicol or gentamicin eye drops. Neonates with systemic upset (32%) received intravenous antibiotics. A variety of common micro-organisms such as *Acinetobacter*, *Enterobacter*, and *Haemophilus influenzae* contributed to a few cases of neonatal conjunctivitis.

Ophthalmological consultations were arranged for all cases with culture-positive chlamydial conjunctivitis during hospitalisation and followed up after discharge from hospital. None of them developed any complications related to chlamydial infection. At 6-month follow-up, no pyloric stenosis was noted in those neonates prescribed oral erythromycin.

The presence of blood-stained discharge was a highly specific sign of chlamydial conjunctivitis with specificity of 100% and a positive predictive value of 100% (Table 3). Periorbital oedema was also highly specific (82%) for chlamydial infection.

Discussion

Staphylococcus aureus was the most common organism cultured from neonates with acute conjunctivitis, but its role in neonatal conjunctivitis remains controversial: it

Table 2. Causative organisms in conjunctivitis

Organism	Occurrence, n=90 No. (%)
Staphylococcus aureus	32 (36)
Chlamydia trachomatis	19 (21)
Escherichia coli	15 (17)
Acinetobacter	5 (6)
Enterobacter	5 (6)
Serratia marcescens	3 (3)
Haemophilus influenzae	2 (2)
Klebsiella	2 (2)
Branhamella catarrhalis	2 (2)
Actinobacillus	1 (1)
Neisseria gonorrhoeae	1 (1)
Group B streptococci	1 (1)
Haemophilus parainfluenzae	1 (1)
Corynebacterium macginleyi	1 (1)
Total	90 (100%)

is frequently cultured from the eyes of asymptomatic neonates.[11] *Chlamydia trachomatis* was the second most common causative organism in acute neonatal conjunctivitis in our series. *Chlamydia trachomatis* is an obligate gram-negative, intracellular bacterium that lacks the ability to reproduce independently. It can only reproduce within the host cells. It is always pathogenic and is not part of the normal flora of the urogenital tract although urogenital infection is often asymptomatic. It infects and disrupts the epithelial tissues but does not seem to invade or destroy deeper tissues or organs.[12] In newborns, several sites may be inoculated with chlamydia during passage through the infected maternal cervix at delivery. These sites include the eyes, nasopharynx, rectum, and vagina. The infant may also aspirate infected secretions with its first breath. Definite diagnosis can be made by isolating the organism in tissue culture because this obligate intracellular organism to be cultured in a medium containing epithelial cells, not just exudate.[13] Acquisition occurs in about 50% of neonates born vaginally to infected mothers.[14,15] The risk of conjunctivitis is 25% to 50% and of pneumonia, 5% to 20%.[13] Pregnant women may be asymptomatic, or present with vaginal leukorrhoea, puerperal endometritis, miscarriage, or preterm labour.[16]

In the United States, chlamydial infection is the most common sexually transmitted infection and the highest rate is among sexually active adolescents and young adults.[17] Prevalence of this organism in pregnant women varies among different countries, but has been reported to be between 6% and 12% in the United States, and between 10.8% and 35.9% in Mainland China.[13,14,16] Such figures may nonetheless be underreported since a lack of medical staff awareness and laboratory support means that not all cases of neonatal conjunctivitis are fully investigated. The true prevalence of chlamydia in Hong Kong is largely unknown and it is not screened for as part of routine antenatal care. In this series, all parents of neonates with chlamydial conjunctivitis denied any history or related symptoms of STD. This may have been due to the stigma in Chinese culture and society associated with having an STD.[18] A family history of STD or related symptoms are thus not reliable indicators of the true prevalence of chlamydia infection in Hong Kong.

In this series, the median age of presentation for chlamydial conjunctivitis was day 7 of life. This is contrary to previous epidemiological data that suggest an insidious onset towards the second week of life and more like gonococcal conjunctivitis that presents earlier in the first 2 to 5 days of life.[19] There was also significant overlap with the onset of other bacterial conjunctivitis. The day of onset of eye discharge thus did not directly indicate chlamydial infection.

In clinical practice, treatment is generally commenced before microbiological results are available. Positive cultures are not usually available before 72 hours and immunofluorescence results take 36 to 48 hours. Other research tools, for example, polymerase chain reaction and ligase chain reaction, that can detect *C trachomatis* have been used for tracking vertical transmission.[6,20] While these tests are more sensitive and in many cases more specific than conventional laboratory methods, they have not replaced the less sensitive technologies (eg immunofluorescence) because of their prohibitively high cost and the need for laboratory support.[21] Doctor's clinical judgement and experience of deciding when to refer suspected chlamydial infection remain the mainstay of detection.

In this study, maturity, sex, growth variables, and presence of systemic upset were similar in both groups. Blood-stained eye discharge nonetheless appeared to be specific for chlamydial conjunctivitis, with a high specificity and high positive predictive value. When neonates with blood-stained eye discharge were treated as chlamydial conjunctivitis before culture results were available, none of

Table 3. Presence of blood-stained discharge and periorbital oedema in chlamydial conjunctivitis

	Presence of blood-stained discharge (95% CI)	Presence of periorbital oedema (95% CI)
Sensitivity	32% (11-52%)	89% (74-100%)
Specificity	100% (100%)	82% (73-91%)
Positive predictive value	100% (100%)	55% (37-73%)
Negative predictive value	85% (77-92%)	97% (92-100%)

them were over-treated as chlamydial infection. The presence of periorbital oedema also showed high sensitivity (89%) and high specificity (82%) to predict chlamydial conjunctivitis.

The actual mechanism of haemorrhage in cases of chlamydial infection is unknown. Conjunctiva, which is a thin translucent mucous membrane, contains non-keratinising, squamous epithelium and a thin, richly vascularised substantia propria (containing lymphatic vessels and cells, such as lymphocytes, plasma cells, mast cells, and macrophages). It can be divided into three parts, based on location: bulbar, palpebral, and fornix. Any causes of inflammation of the conjunctiva may cause blood vessel dilation, chemosis, and excessive secretion, and lead to various symptoms and signs. The chlamydial conjunctivitis in neonates would induce inflammation and neovascularisation of conjunctiva and cornea, similar to hallmarks of active trachoma in older children and adults. It has been established that follicular reaction does not occur in newborns prior to 6 to 8 weeks of life because the requisite lymphoid tissue is absent with a consequent lack of local conjunctiva immunity.[1] In addition there are no tears at birth. These two factors aggravate the inflammatory response of conjunctiva and lead to blood vessel dilation, chemosis, and excessive secretion.[22,23] The clinical features of chlamydial conjunctivitis in the neonatal period thus tend to be more serious than in other age-groups. It remains unclear why blood-stained eye discharge is specific to chlamydial infection but not to other kinds of bacterial infection, especially gonorrhoea. One possible explanation may relate to the different parts of conjunctiva affected. Chlamydial infection affects the bulbar and palpebral parts of the conjunctiva that comprises more blood vessels than the fornical parts[24] and subsequently tends to exhibit a greater inflammatory response with more bleeding.

The standard treatment of proven chlamydial conjunctivitis or pneumonia is a 14-day course of oral erythromycin (50 mg/kg per day in four divided doses). Treatment must be aimed not only at ocular colonisation, but at eradication of nasopharyngeal carriage and the possible subsequent development of *C trachomatis* pneumonia.[13] Neither 1% silver nitrate nor erythromycin topical eye drops should be used because they do not eradicate nasopharyngeal carriage.[9] Moreover, late sequelae of corneal neovascularisation and conjunctival scarring have been observed more often in infants with chlamydial conjunctivitis treated with topical antibiotics than those treated with oral erythromycin.[24]

In some studies, an increased risk of infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks being prescribed oral erythromycin for pertussis prophylaxis.[25] This association was also seen in a retrospective cohort study in which an 8-fold increased risk of pyloric stenosis was associated with exposure to erythromycin between 3 and 13 days of age.[26] In our study, no neonate had developed any complications related to erythromycin treatment by 6-month follow-up. Medical staff need to inform parents of the potential risk of infantile hypertrophic pyloric stenosis before prescribing erythromycin.

Long-term ocular sequelae following successful treatment of chlamydial conjunctivitis are extremely rare.[1] Blindness, if it occurs, is not due to corneal involvement (seen in gonococcal conjunctivitis), but to eyelid scarring and pannus formation (as in trachoma). Nonetheless, trachoma, which is a chronic follicular keratoconjunctivitis, does not occur in newborns because of the lack of follicular reaction. It remains controversial whether routine follow-up should include cultures from the eyes, nasopharynx, rectum, and vagina to confirm eradication of chlamydia.[24]

Conclusion

Chlamydia trachomatis was the second most common cause of acute neonatal conjunctivitis after *S aureus*. The presence of haemorrhagic discharge was a highly specific sign of neonatal chlamydial infection. The concomitant presence of periorbital oedema should alert general practitioners or paediatricians to the possibility of chlamydial conjunctivitis. Early referral and prompt treatment with oral erythromycin is safe and effective.

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