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REGULAR ARTICLE

Aetiology of neonatal conjunctivitis evaluated in a population-based setting

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ABSTRACT

Aim: Our aim was to study prospectively the aetiology of neonatal conjunctivitis in a population-based setting.

Methods: Altogether 173 neonates with clinical conjunctivitis aged on average 20 (SD 10) days were recruited from child welfare clinics in Oulu, Finland, in 2010–2015. Conjunctival specimens were collected from 167 neonates for multiplex polymerase chain reaction to detect 16 respiratory viruses, from 163 for polymerase chain reaction to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* and from 160 for bacterial culture studies. The cases were followed up until the age of 18 months.

Results: Viral conjunctivitis was diagnosed in 8/167 (4.8%; 95% CI 2.1–9.2%), chlamydial or gonococcal conjunctivitis in 0/163 cases (0%; 95% CI 0–2.2%) and other bacterial conjunctivitis in 58/160 (36%; 95% CI 29–44%). Rhinovirus was found at the ocular site in 4/167 (2.4%) neonates, adenovirus in 3/167 (1.8%) and bocavirus in 1/167 (0.6%). The most commonly isolated bacteria included *Staphylococcus aureus* (16%), *Moraxella catarrhalis* (9.4%) and *Streptococcus pneumoniae* (3.1%). None of these pathogens was associated with the 4/173 (2.3%) cases later operated on for persistent nasolacrimal duct obstruction.

Conclusion: *Chlamydia trachomatis* was a rare pathogen in neonatal conjunctivitis in a population-based setting, but respiratory viruses were detected more frequently than indicated earlier.

INTRODUCTION

Conjunctivitis is a common disease during the first month of life (1–6), and anatomical problems such as congenital nasolacrimal duct obstruction, which affects 5–6% of all neonates and infants (7), are considered to have a significant role in its neonatal pathogenesis. *Chlamydia trachomatis* (*C trachomatis*) and *Neisseria gonorrhoeae* (*N gonorrhoeae*) are the most significant bacterial pathogens to be diagnosed in infectious neonatal conjunctivitis, because without treatment they can both lead to serious long-term consequences (8). *C trachomatis* is considered a major causative agent for neonatal conjunctivitis in many centres (9–11), but its proportion varies greatly between geographical regions and clinical settings, ranging from 0 to 64% (1–4,6,9–18). Respiratory viruses cause more than 10% of acute paediatric conjunctivitis (19), but their role during the neonatal period remains unclear.

Primary care physicians do not often perform thorough microbiological tests for neonatal conjunctivitis in communities where gonococcal conjunctivitis is rare and it is thus unclear whether systematic testing for pathogens, including *C trachomatis*, should be performed in all uncomplicated cases of neonatal conjunctivitis in primary care. We set out to study the proportions of respiratory viruses, *C trachomatis*, *N gonorrhoeae* and other bacteria in neonatal conjunctivitis in a population-based setting. In addition, we aimed

Abbreviations
C trachomatis, *Chlamydia trachomatis*; CI, Confidence interval; *N gonorrhoeae*, *Neisseria gonorrhoeae*; PCR, Polymerase chain reaction.

Key notes

- The aetiology of neonatal conjunctivitis has not been studied in a population-based setting using modern polymerase chain reaction methods.
- *Chlamydia trachomatis* was a rare pathogen in neonatal conjunctivitis in a population-based setting, but respiratory viruses were detected significantly more frequently than indicated earlier.
- Our findings suggest that it is important to be aware of the local aetiology of neonatal conjunctivitis, as causative agents vary between geographical locations and clinical settings.

to evaluate whether early neonatal conjunctivitis caused by certain pathogens results in persistent nasolacrimal duct obstruction in infancy.

PATIENTS AND METHODS

Study design and population

We investigated prospectively the aetiology of neonatal conjunctivitis and the proportions of respiratory viruses, *C trachomatis*, *N gonorrhoeae* and other bacteria in ten child welfare clinics in the city of Oulu, Finland, from October 12, 2010, to September 25, 2015. The research plan was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland (EETTMK 43/2010). More than 99% of the children in Finland attend child welfare clinics for regular health examinations, so that it may be said that these clinics assess the physical, mental and social growth and development of all children from newborn infants to seven years of age (20). A public health nurse makes a postpartum home visit one to two weeks after birth, and the first follow-up appointment at a child welfare clinic is at the age of one month.

We included all neonates who had symptomatic conjunctivitis, defined as the presence of conjunctival discharge, erythema or swelling of the eyelids before the age of 30 days, in this study. Parents or legal guardians were informed and a written consent was obtained. Parents or legal guardians were asked to complete a structured questionnaire concerning demographic data, symptoms and signs of conjunctivitis, symptoms and signs of possible respiratory infection and the onset of the symptoms. As a follow-up, we reviewed the medical records of these cases at Oulu University Hospital, including the Department of Ophthalmology, at least until the age of 18 months, to find out whether there were any long-term ocular consequences of neonatal conjunctivitis. In addition, to estimate the coverage of our study, we retrieved all microbiologically confirmed diagnoses of *C trachomatis* in neonates within the first 30 days of life in the same catchment area.

Maternity clinics in Finland provide prenatal care and regular health examinations for women during pregnancy (21). Pregnant women have approximately 13 appointments with a public health nurse and three with a doctor during each pregnancy, but they are not routinely screened for genital *C trachomatis* or *N gonorrhoeae* infections, as a first-catch urine test is performed only upon some suspicion of sexually transmitted infection, that is symptoms or a history of sexually transmitted disease. One screening study of the prevalence of *C trachomatis* positivity in Finnish pregnant women, including asymptomatic cases, based on nucleic acid in a first-void urine sample, estimated this figure to be 2.7% (22). As *N gonorrhoeae* positivity in the general population is low (0.06%) (23), ocular prophylaxis against *N gonorrhoeae* is not routinely provided for neonates in Finland.

Conjunctival specimens

We trained public health nurses working in the maternity and child welfare clinics concerned to obtain conjunctival specimens. We also prepared an instruction video and a laminated instruction sheet about sampling and distributed these to the nurses. The specimen collection materials were packed in ready-to-use sets beforehand. Transystem M40 transport cotton-tipped swabs (Copan Diagnostics, Inc, California, USA) were used for bacterial culture and Abbott multi-Collect Specimen Collection Swabs (Abbott Molecular Inc, Illinois, USA) and FLOQSwabs Copan flocked swabs (Copan Diagnostics, Inc, California, USA) for polymerase chain reaction (PCR) testing. Conjunctival specimens were collected from the actual site of infection and from both eyes in cases of bilateral conjunctivitis. First, the area around the affected eye was gently cleansed to remove discharge, after which the culture was obtained by swabbing the mucosal area of the lower eyelid. Second, the inner surface of the lower eyelid was swabbed thoroughly two to three times to collect epithelial cells for nucleic acid amplification testing. The swabs were stored and transported at room temperature to the clinical microbiological laboratory at Oulu University Hospital (NordLab, Oulu, Finland) on the same day. Sheep blood agars at a concentration of 5% and chocolate agars were used to culture the bacteria. A multiplex real-time PCR was used to detect respiratory viruses, including adenovirus, bocavirus, enterovirus, influenza viruses A and B, coronaviruses 229E, NL63 and OC43, human metapneumovirus, parainfluenza viruses 1, 2, 3 and 4, respiratory syncytial viruses A and B and rhinovirus. The nucleic acid was isolated for respiratory viruses using the QS DPS Virus/Pathogen Mini Kit (Qiagen, Hilden, Germany) and a Qiagen Symphony SP instrument (Qiagen, Germantown, USA) and amplified and detected using a Seegene Anyplex RV16 Kit (Seegene Inc, Seoul, Korea) and the CF96TM Real-Time PCR System (Bio-Rad Laboratories Inc, California, USA). PCR was used to detect *C trachomatis* and *N gonorrhoeae*, for which nucleic acid was isolated using the Abbott mSample Preparation System DNA Reagent (Abbott Molecular Inc, Illinois, USA) and the Abbott m2000s instrument (Abbott Molecular Inc, Illinois, USA) and amplified and detected using an Abbott RealTime CT/NG Amplification Reagent Kit (Abbott Molecular Inc, Illinois, USA) and Abbott m2000rt instrument (Abbott Molecular Inc, Illinois, USA). Positive *C trachomatis* and *N gonorrhoeae* findings were immediately reported to the physicians. Other microbiological findings were available to the primary care physicians as needed.

Classification of micro-organisms as pathogens and commensals

We classified *Bacillus cereus,* group A and B streptococci, *C trachomatis*, *Corynebacterium* species, *Enterococcus faecalis*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca, Moraxella catarrhalis, N gonorrhoeae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus mitis* and *Streptococcus pneumoniae* as pathogens,

whereas coagulase-negative staphylococci, alpha-haemolytic streptococci and *Acinetobacter* species were classified as non-pathogens (24). All respiratory viruses were classified as pathogens.

Sample size calculation

We regarded it as clinically significant, that is the obtaining of routine conjunctival samples for *C trachomatis* would be needed, if 5% (accuracy ±2.5%) of neonatal conjunctivitis cases in a population-based setting were to be caused by *C trachomatis*. With a two-sided α error of 0.05, 226 infants with conjunctivitis would have been needed to this level. As chlamydial conjunctivitis was very rare in our population (0/163), after five years of recruitment, we calculated the 95% confidence interval (CI) for the proportion of *C trachomatis* conjunctivitis among all neonatal conjunctivitis cases, which was 0 to 2.2% and then completed the study, as we had achieved the targeted accuracy.

Statistical analysis

The statistical analyses were performed using SPSS version 24 software (SPSS Inc, Chicago, Illinois, USA), and the sample size and 95% CIs of the proportions were calculated using StatsDirect statistical software (25). Fisher's exact test was used to compare the differences between symptoms and bacterial culture findings. A p-value < 0.05 was considered statistically significant.

RESULTS

There were 9600 births in the catchment area during the period concerned, and we identified 173 neonates with clinical conjunctivitis, representing 1.8% of these. The mean age of the mothers was 29 (SD 5.3) years, and 20% of them were aged 24 years or younger. Primigravidae accounted for 48% of the mothers.

Conjunctival symptoms appeared at an average age of 7.3 (SD 7.0) days. Mucopurulent discharge from one or both eyes was present in 164 of 173 cases (95%), swelling of the eyelids in 52 (30%) and redness in 42 (24%). None of the neonates had blood-stained discharge. Altogether 74 (43%) neonates had bilateral conjunctivitis. Other respiratory symptoms were detected in 33 (19%), of whom 23 (13%) had rhinorrhoea, six (3.5%) coughing, three (1.7%) nasal congestion and one (0.6%) sneezing.

The neonates were 20 (SD 10) days old on average when the conjunctival samples were collected. A *C trachomatis* and *N gonorrhoeae* PCR was obtained from 163/173 (94%) of them, a respiratory virus multiplex PCR from 167 (97%) and a bacterial culture from 160 (92%) (Table 1).

A multiplex PCR for any respiratory virus from the ocular site was positive in 8/167 cases (4.8%; 95% CI 2.1–9.2%) (Table 1), of which four were rhinovirus, three adenovirus and one bocavirus. Concurrent bacterial growth was detected in half (4/8) of these cases, as *Moraxella catarrhalis* was isolated in one sample together with rhinovirus and in one with bocavirus and *Staphylococcus epidermidis* was isolated in one sample together with rhinovirus and one with adenovirus. Altogether two of the eight neonates (25%) with viral conjunctivitis had respiratory tract symptoms reported by the parents or legal guardians.

Table 1 Microbiological findings in 173 cases of neonatal conjunctivitis

Microbiological findings	Number of neonates	Proportion
Respiratory virus detection	N = 167	% (95% CI)
Any respiratory virus	8	4.8 (2.1–9.2)
Rhinovirus*	4	2.4 (0.7–6.0)
Adenovirus	3	1.8 (0.4–5.2)
Bocavirus*	1	0.6 (0.02–3.2)
Coronaviruses	0	0 (0–2.2)
Human metapneumovirus	0	0 (0–2.2)
Influenza viruses	0	0 (0–2.2)
Parainfluenza viruses	0	0 (0–2.2)
Respiratory syncytial virus	0	0 (0–2.2)
Chlamydia trachomatis and *Neisseria gonorrhoeae* detection	N = 163	% (95% CI)
Chlamydia trachomatis	0	0 (0–2.2)
Neisseria gonorrhoeae	0	0 (0–2.2)
Bacterial culture	N = 160	% (95% CI)
Pathogens†	58	36 (29–44)
Staphylococcus aureus	25	16 (10–22)
Moraxella catarrhalis	15	9.4 (5.3–15)
Corynebacterium species	6	3.8 (1.4–8.0)
Streptococcus pneumoniae	5	3.1 (1.0–7.1)
Haemophilus influenzae	4	2.5 (0.7–6.3)
Bacillus cereus	1	0.6 (0.02–3.4)
Escherichia coli	1	0.6 (0.02–3.4)
Enterococcus faecalis	1	0.6 (0.02–3.4)
Group B streptococcus	1	0.6 (0.02–3.4)
Klebsiella oxytoca	1	0.6 (0.02–3.4)
Pseudomonas aeruginosa	1	0.6 (0.02–3.4)
Streptococcus mitis	1	0.6 (0.02–3.4)
Non-pathogenic bacterial growth‡	25	16 (10–22)
Normal mixed microbial flora	67	42 (34–50)
Negative culture	8	5.0 (2.2–9.6)

*2/8 infants had *Moraxella catarrhalis* in addition to viruses in their eye specimens.
†4/58 infants had two bacterial pathogens in their eye specimens.
‡The most common non-pathogens were coagulase-negative staphylococcus (N = 28) and alpha-haemolytic streptococcus (N = 10).
CI, Confidence interval.

None of the neonates tested (0/163) had *C trachomatis* or *N gonorrhoeae* nucleic acid in their conjunctival specimens (95% CI 0–2.2%) (Table 1), and no cases of chlamydial or gonococcal neonatal conjunctivitis were diagnosed outside this study within the catchment area, as indicated by a review of the microbiological laboratory database for the relevant period. Bacterial pathogens other than *C trachomatis* or *N gonorrhoeae* were cultured from the conjunctivae of 58/160 (36%) neonates (95% CI 29–44%) (Table 1), the most commonly identified ones being *Staphylococcus aureus* (16%), *Moraxella catarrhalis* (9.4%), *Corynebacterium* species (3.8%), *Streptococcus pneumoniae* (3.1%) and *Haemophilus influenzae* (2.5%). Non-pathogenic bacterial growth was detected in 25 (16%)

neonates (95% CI 10–22%), the most commonly identified being coagulase-negative staphylococci and alpha-haemolytic streptococci. A normal mixed microbial flora of the conjunctiva was present in 67 (42%) neonates (95% CI 34–50%), and eight bacterial cultures (5.0%) were negative (95% CI 2.2–9.6). There were no statistically significant associations between the symptoms and the findings in the bacterial cultures from the conjunctivae (Table 2).

Altogether 4/173 (2.3%) infants and toddlers suffered from persistent nasolacrimal duct obstruction, and they were treated with either probing or surgery at the median age of 17 months (range 9–36). Of these children, two had *Moraxella catarrhalis* in their eye specimens taken in infancy, one had *Staphylococcus aureus* and one had a negative culture. There were no other long-term ophthalmological consequences recorded in the children's medical records after neonatal conjunctivitis.

DISCUSSION

It can be concluded from the present prospective study that *C trachomatis* was a rare pathogen in neonatal conjunctivitis in this population-based setting. However, respiratory viruses were detected significantly more frequently than have been indicated earlier. None of the pathogens detected in the neonates was associated with persistent nasolacrimal duct obstruction.

Only a few studies have previously investigated the viral aetiology of neonatal conjunctivitis (11,14). Sandström et al. and Rapoza et al. reported only one case of viral neonatal conjunctivitis each (1/100 and 1/55), the causative agents being Coxsackie virus A9 and Herpes simplex virus type 1 (11,14). Both studies originate from the 1980s, when the current novel multiplex PCR methods for detecting common respiratory viruses were not yet available. The Red Book, 2015 Report of the Committee on Infectious Diseases, American Academy of Pediatrics, does not mention common respiratory viruses as causative agents for neonatal conjunctivitis (24); however, such viruses were found in 5% of our neonates with clinical conjunctivitis when using modern multiplex PCR methods, thus providing support that a viral aetiology should also be considered during the neonatal period. Altogether two neonates with viral conjunctivitis had a concurrent bacterial pathogen in their conjunctival specimens, but even after excluding these cases, the proportion of viral conjunctivitis remained at 4%.

Mucopurulent discharge, conjunctival redness and swollen eyelids have been observed as distinctive symptoms of chlamydial conjunctivitis (10,12,26). Chang et al. reported that 32% of the infants in their patient series who were suffering from vertically transmitted chlamydial conjunctivitis had blood-stained discharge from the infected eyes (27). We showed in a previous register-based nationwide study in Finland that vertically transmitted *C trachomatis* infections in children were rare (28), and we thus assumed that *C trachomatis* infections may be underdiagnosed in the neonatal period. In the present study, however, it transpired that *C trachomatis* was not diagnosed in any of the 163 consecutive neonates with clinical conjunctivitis in a population-based setting. Furthermore, the majority of the present neonates had mild conjunctivitis characterised only by mucopurulent discharge without any other signs of infection, and none of them had blood-stained ocular discharge. Our findings thus indicate that routine testing for *C trachomatis* in an uncomplicated neonatal conjunctivitis in primary care is unnecessary unless the symptoms are severe or prolonged.

The main strength of the present study is that it is one of the first evaluations of both the viral and bacterial aetiology of neonatal conjunctivitis to be conducted in a community setting and one in which the possible long-term consequences of neonatal conjunctivitis could be evaluated, as there is only one centre in the catchment area that provides ophthalmological surgery for infants and children. While the prevalence of persistent nasolacrimal duct obstruction is estimated to be about 4% after the first year of life (29), the occurrence in our study was 2%, which is slightly less but within the range of values reported in the literature. None of the pathogens detected in the present study had any long-term consequences associated with them.

LIMITATIONS

Prior studies have detected respiratory viruses, in particular rhinoviruses, from nasal swab specimens in asymptomatic subjects during the neonatal period (30). Even though

Table 2 Symptoms of neonatal conjunctivitis by bacterial culture and virus PCR findings from the conjunctivae

Symptom	Bacterial pathogen* N = 58 n (%)	Virus N = 8 n (%)	Non-pathogen* N = 25 n (%)	Normal flora[a] N = 67 n (%)	Negative* N = 8 n (%)
Mucopurulent discharge	54 (93)	8 (100)	23 (92)	64 (96)	8 (100)
Redness	16 (28)	3 (38)	7 (28)	16 (24)	1 (13)
Swelling	20 (34)	3 (38)	5 (20)	22 (33)	2 (25)
Rhinorrhea	12 (21)	2 (25)	4 (16)	5 (7)	0 (0)
Cough	2 (3)	0 (0)	0 (0)	4 (6)	0 (0)
Nasal congestion	0 (0)	0 (0)	1 (4)	2 (3)	0 (0)
Sneezing	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)

*Symptoms did not differ between the bacterial culture findings ($p > 0.05$).
PCR, Polymerase chain reaction.

respiratory viruses are likely to be pathogens when found at the ocular site, we cannot confirm that the viruses detected here caused the conjunctival symptoms in all subjects with a positive virus PCR. Furthermore, we did not evaluate the sensitivity of multiplex real-time PCR for conjunctival specimens, and therefore, the true occurrence of respiratory viruses could have been underestimated in this study. Finally, this research was conducted in a country with excellent standards of maternity care, which impairs the generalisability of the results to countries with poor maternity care.

CONCLUSION

We conclude that *C trachomatis* was a rare pathogen in neonatal conjunctivitis in a population-based setting, but respiratory viruses were detected more frequently than indicated earlier. Our findings suggest that it is important to be aware of the local aetiology of neonatal conjunctivitis, as causative agents vary between geographical locations and clinical settings (1–4,6,9–18). Even though systematic sampling in primary care for all possible pathogens appears to be unnecessary in our setting, routine sampling may still be needed in secondary and tertiary care units and in some geographical locations.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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