Introduction

Ophthalmia neonatorum (ON), also called neonatal conjunctivitis, is an acute mucopurulent infection of the conjunctivae occurring within 28 days of life. It is a relatively common disease affecting 1.6% to 12% of all newborn infants with an increase up to 23% in developing countries. ON can be divided into noninfectious and infectious categories. The most common noninfectious cause is chemical conjunctivitis whilst the infectious category includes bacterial, chlamydial and viral infections with chlamydia being the most common. Affected newborns present with a purulent, mucopurulent or mucoid discharge from one or both eyes, injected conjunctiva and lid swelling. In some cases there may also be an association with systemic infection. The time of onset of conjunctivitis as well as conjunctival scraping can aid in the diagnosis of the specific aetiology. A number of prophylactic antibiotic or antiseptic agents have been used to prevent ON namely 1% silver nitrate ophthalmic drops, 0.5% erythromycin or 1% tetracycline ophthalmic ointment and recently a 2.5% povidone-iodine ophthalmic solution. Despite this fact ON still remains a significant cause of ocular morbidity, blindness and even death in underdeveloped countries. The organisms causing ON are transmitted mainly from the mother’s birth canal during delivery. In countries where the incidence of ON is very low, an alternative prophylaxis strategy is the introduction of prenatal screening and treatment of infected mothers, forgoing routine neonatal prophylaxis and conducting a follow-up of infants after birth for the possible development of infection.

Generally ON can be divided into noninfectious and infectious categories. The most common noninfectious is chemical conjunctivitis whilst the infectious category includes bacterial, chlamydial and viral causes with chlamydia being the most common. Furthermore infectious agents which the infant may acquire as it passes through the birth canal include Streptococcus sp., Staphylococcus sp., Escherichia coli, Pseudomonas sp., Klebsiella pneumoniae, Haemophilus sp., Neisseria gonorrhoea, and herpes simplex. The time of onset of conjunctivitis as well as conjunctival scraping can aid in the diagnosis of the specific aetiology of the neonatal conjunctivitis (Table 1). In differential diagnosis of ocular inflammation in infants dacryocystitis neonatorum and preseptal cellulitis also need to be taken into consideration.

ON is considered as an ophthalmic emergency. The neonatal conjunctivitis is particularly vulnerable to infection due to the lack of immunity and the absence of local lymphoid tissue at birth. Affected newborns present with a purulent, mucopurulent or mucoid discharge from one or both eyes within the first month of life and typical symptoms of injected conjunctiva and lid swelling. In some cases there may also be an association with systemic infection which further endangers the infant. Since most cases of infectious conjunctivitis occur due to transfer of infection in the birth canal during delivery the presence of STDs in the mother is the main risk factor for gonococcal or chlamydial ON. However the infection may also be spread by people...
Incidence

Now days Chlamydia is the most common single cause of infective neonatal conjunctivitis accounting for 2–40% of cases whilst Neisseria gonorrhoeae is reported in less than 1% of cases. Incidence of these two pathogens has notably declined in the last two decades as a result of decreased prevalence of STD in the population and the improvement of prenatal screening and care. Herpes simplex is the cause of ON in less than 1% of cases whilst non-sexually transmitted bacteria such as Staphylococcus, Streptococcus, Haemophilus species and other Gram-negative bacteria account for the majority of the remaining ON cases (30–50%). Apart from the infectious forms ON also includes chemically induced conjunctivitis occurring in 10–90% of newborns who have been subjected to the instillation of prophylactic agents mostly silver nitrate. Cases of chemical conjunctivitis are decreasing as silver nitrate prophylaxis or with other agents such as erythromycin or tetracycline. Chemical conjunctivitis accounts for most cases of ON presenting with mild irritation, tearing and redness within the first 24 hours of life. It is most commonly associated with silver nitrate prophylaxis or with other agents such as erythromycin or tetracycline. Chemical conjunctivitis is a self-limiting condition with spontaneous resolution in 2 to 3 days and as such does not require any diagnostic tests or treatment. However, some favour the use of preservative free artificial tears or even antibiotic solution topically in order to prevent secondary infection.

Laboratory tests

Laboratory studies for neonatal conjunctivitis are essential for proper management and diagnosis. Samples for testing should be obtained from the inner side of the eyelid after its eversion. Sample the exudates is not adequate since this technique increases the risk of a false-negative test result. Initial culture on chocolate agar or a Thayer-Martin test for Neisseria gonorrhoeae should be obtained as well as blood agar for other bacteria. Chlamydial infection can be ruled out using conjunctival scraping Giemsa stain for intracytoplasmic inclusion bodies or direct immunofluorescent antibody assay. Diagnostic tests which reveal bacterial genomes based on polymerase chain reactions are also available and useful in laboratory testing. In herpetic conjunctivitis Gram stain may reveal multinucleate giant cells and Papanicolaou smear may show eosinophilic intranuclear inclusions in epithelial cells. Culture for herpes simplex virus can also be beneficial for diagnostic purposes.

Clinical features and treatment

Chemical conjunctivitis

Chemical conjunctivitis accounts for most cases of ON presenting with mild irritation, tearing and redness within the first 24 hours of life. It is most commonly associated with silver nitrate prophylaxis or with other agents such as erythromycin or tetracycline. Chemical conjunctivitis is a self-limiting condition with spontaneous resolution in 2 to 3 days and as such does not require any diagnostic tests or treatment. However, some favour the use of preservative free artificial tears or even antibiotic solution topically in order to prevent secondary infection.
Gonorrhoeal infection

Neisseria gonorrhoeae accounts for less than 1% of all reported cases of ON.7 In the absence of adequate prophylaxis, 30% to 42% of infants born by vaginal delivery to infected mothers will develop gonococcal ON and the transmission rate is even higher in mothers with concomitant chlamydial infection.2,6

The disease typically presents with profound chemosis, edema of the eyelids and abundant purulent discharge that may be blood-tinged from superficial hemorrhage within 2 to 5 days of birth; however, it may manifest even up to 2 to 3 weeks after delivery.6,7 It is an established fact that Neisseria gonorrhoeae may penetrate intact corneal epithelium causing rapid ulceration and perforation.7 Thus if left untreated gonorrheal ON may lead to corneal scarring, ulceration, panophthalmitis and perforation of the globe within 24 hours.5,7 Therefore acute neonatal conjunctivitis should initially be treated as gonococcal until culture test results become available, after which time the treatment can be modified based on the laboratory findings.1,3

Infants with gonorrheal ON should be hospitalized and separated from other babies, treated with frequent irrigation of the conjunctiva and topical bacitracin or erythromycin ophthalmic ointment every 2 to 4 hours. However, topical penicillin is usually unreliable due to resistance; if sensitivity is established, penicillin drops should also be used. In the case of corneal involvement topical atropine is applied. Due to the high prevalence of penicillin-resistant Neisseria gonorrhoeae, the treatment choice for this organism is a systemic, third-generation cephalosporin such as ceftriaxone 25 to 50 mg/kg per day in divided doses administered intravenously (i.v.) or intramuscularly (i.m.) to a maximum dose of 125 mg during a 7 day period. In addition, a single dose of cefotaxime 100 mg/kg i.m. may represent an alternative treatment. Infants with gonorrheal ON should be mandatorily evaluated for disseminated gonococcal disease such as arthritis, sepsis and meningitis.1,3,4 The parents should also be evaluated and treated for gonorrhea.1 Infants born to mothers with known gonococcal infection or no prenatal care should be treated for presumptive infection regardless of the absence of visible signs with a single parenteral dose of cefotaxime 100 mg/kg or ceftriaxone 25–50 mg/kg to a maximum dose of 125 mg.5,7,17,18

Bacterial conjunctivitis

Non–sexually transmitted bacteria account for 30% to 50% of cases of ON and usually have a longer incubation period compared to other infectious causes.3–5 They generally present with a subacute onset between the 4th and 28th day of life. Depending on the pathogen there may be a diverse clinical picture of a red eye with lid swelling and a varying amount of purulent discharge. Specific treatment for infectious neonatal conjunctivitis is based on the clinical and laboratory findings on Gram, Giemsa and Papanicolaou stains.1,3

Most bacterial conjunctivitis respond quickly to topical antibiotic treatment; erythromycin or bacitracin ointment for gram-positive organisms; gentamicin or tobramycin drops and ointment for gram-negative organisms; and established topical antibiotics for Pseudomonas.1,3,19 Antibiotic choice may be altered once culture and sensitivity results become available. In cases of corneal involvement as seen with virulent organisms such as Pseudomonas fortified topical antibiotics are administered and often supplemented by systemic treatment. ON caused by Pseudomonas is rare but can present with eyelid edema, erythema and purulent discharge potentially causing corneal perforation, endophthalmitis, blindness, and even possibly death. Presumptive diagnosis can be made using the Gram stain test whilst a definite diagnosis is based on conjunctival culture tests.3,4 Systemic antibiotics have poor penetration into the anterior chamber of the eye and thus in a case of Pseudomonas infection both systemic and topical amnoglycoside antibiotics and in some instances subconjunctival injections are required for effective treatment.3,4,19

Chlamydial infection

Chlamydial conjunctivitis has a later onset with less severe symptoms than gonococcal. It typically occurs unilaterally or bilaterally from 5 to 14 days after birth or earlier if membranes rupture prematurely.1,3,20 The clinical manifestations vary from mild conjunctival injection with scant watery to severe mucopurulent discharge with eyelid edema, chemosis and pseudomemone formation.6,10 Loss of vision is very rare. Most cases of chlamydial infections resolve spontaneously without complications however if left untreated superficial corneal vascularization and conjunctival scarring may occur.10 Chlamydial conjunctivitis may also be associated with preseptal cellulitis and less commonly rhinitis, otitis and pneumonitis. It has been estimated that 2–24% of pregnant women have chlamydial cervicitis and that 18–50% of infants born to these mothers develop conjunctivitis whilst 15–20% of infants develop nasopharyngeal infection and 3–18% pneumonia due to C. trachomatis.20

Newborns with conjunctivitis should have specimens of their conjunctiva and pharynx sent for culture where diagnosis is made by observing intracytoplasmic inclusion bodies by Giemsa stain or direct immunofluorescent assay. Polymerase chain reaction is also a reliable and efficient test used to prove Chlamydial infection.1,3,20,21 Treatment of chlamidial conjunctivitis includes both topical erythromycin ointment and oral erythromycin 25 to 50 mg/kg per day divided into four doses. Typical treatment lasts for 2 weeks in order to prevent recurrence and secondary pneumonitis.1,9,20 Erythromycin reports a 20% to 30% failure rate and thus some infants require a second or occasionally a third course of antibiotic treatment. Topical treatment alone is inadequate; since it is unable to eliminate concurrent nasopharyngeal infection and unnecessary when sys-

temic treatment is given. A small study has demonstrated that a short course of oral azithromycin (20 mg/kg once daily for 3 days) may be an effective treatment alternative; however further studies are most definitely necessary. Both parents should also be treated for chlamydia even if they are asymptomatic. Appropriate initial therapy for Chlamydial conjunctivitis prior to or in the case of inconclusive results from Gram staining, is broad-spectrum antibiotic such as ofloxacin 0.3% four times a day for a week or until the microbiological results become available.

**Viral conjunctivitis**

Viral conjunctivitis is most commonly caused by adenovirus and herpes simplex virus (HSV). Infants with adenovirus ON might present with petechial hemorrhage or occasionally with large subconjunctival hemorrhages and associated lymphadenopathy in approximately 50% of cases.

Herpetic conjunctivitis may be the sole manifestation of a neonate infected with HSV. Most cases of herpetic conjunctivitis are caused by type II; however up to 30% can be caused by the type I HSV. Onset is acute, usually 1–14 days after birth with unilateral or bilateral serosanguinous discharge and in some cases pathognomonic vesicular skin lesions. Other ocular features may include keratitis, usually presenting as microdendrites or small geographic ulcers, anterior uveitis, cataract, retinitis and in rare cases optic neuritis. Uncommonly, systemic infection can cause jaundice, hepatosplenomegaly, pneumonitis, meningoencephalitis and disseminated intravascular coagulation. Infants with conjunctivitis caused by the HSV may be diagnosed late since they are commonly treated empirically for chlamydial or gonococcal infection.

Infants showing ocular HSV infection should undergo a complete evaluation including lumbar puncture in order to rule out systemic infection. Treatment includes systemic acyclovir 45–60 mg/kg divided into 3 doses per day for a 14 day period coupled with topical ophthalmic solution 1% trifluridine, 0.1% iododeoxyuridine and 3% vidarabine or acyclovir 3% ointment.

**Differential diagnosis**

As mentioned above in differential diagnosis of ON dacryocystitis neonatum and periorbital cellulitis should be considered (Table 2). A blocked nasolacrimal duct is common in newborns resulting in a thick sometimes copious discharge which may be sticky or crusty. This occurs in 6% of neonates and is usually associated with oedema and erythema of the inner canthus. Tearing is common and the conjunctiva is usually not affected. The discharge may be intermittent and responds well to simple cleansing. Purulent drainage can often be expressed from the punctum. Most babies’ ducts clear as they grow with the majority functioning normally by 12 months of age. Periorbital cellulitis is a serious infection preceded by an upper respiratory tract infection. It presents with an acute onset of pronounced eyelid oedema and erythema, epiphora usually accompanied with pain and fever.

**Investigations**

During examination a complete history of previous or concurrent sexually transmitted disease in the mother as well as results of any cervical cultures obtained during pregnancy need to be obtained. Ocular examination with pen light and fluorescein staining of the newborn is a vital part of the procedure. It is important to inspect the cornea in every infant with conjunctivitis in order to rule out corneal involvement. Microbiological investigations should include conjunctival swabs ideally obtained from the everted lid as well as cultures for chlamydial and viral detection. The Gram staining should be conducted urgently in the case of suspicion of gonococcal conjunctivitis.

**Complications**

Potential complications of ON are mainly related to gonococcal conjunctivitis whilst most of the other types of conjunctivitis in the newborn are fairly benign without serious consequences. Gonococcal complications include keratitis, conjunctival scarring and superior corneal pannus. Since Neisseria gonorrhoeae is a very virulent pathogen with the ability to penetrate the intact epithelium it may rapidly cause corneal ulcer and perforation with subsequent endophthalmitis and permanent visual impairment. Side-effects of treatment such as the association between oral erythromycin and infantile hypertrophic pyloric stenosis are rarely reported in infants less than 6 weeks. Further, overwhelming systemic infection such as chlamydial pneumonia or disseminated herpetic simplex may occur. Pseudomonas infection is very rare yet may be devastating, causing keratitis and in disseminated cases ultimately lead to death.

**Prognosis**

Chlamydial infections have good prognosis with 80% of patients showing full recovery after one course of treatment. Bacterial infections with a satisfactory response to medication also have a good prognosis rate.
Table 3. Ocular and systemic complications and consequences of neonatal conjunctivitis

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Ocular complications and consequences</th>
<th>Systemic complications and consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td>None (self limited disease)</td>
<td>None</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Chronic infection may cause corneal scarring and symblepharon (adhesion of eyelid to eye)</td>
<td>Pharyngeal colonization, pneumonitis and otitis media</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Corneal ulceration, perforation and endophthalmitis (may occur within 24 hr of onset)</td>
<td>Meningitis, arthritis, sepsis, and death</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Pseudomonas sp. may cause corneal ulcer, perforation and endophthalmitis</td>
<td>Usually none</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Recurrences throughout life may cause corneal scarring and profound amblyopia. Chorioretinitis, optic neuritis and cataracts also may develop</td>
<td>Meningitis and disseminated CNS disease (mortality rate can be as high as 85%)</td>
</tr>
</tbody>
</table>

CNS – Central Nervous System

Furthermore chemical irritations have good outcome with full spontaneous recovery expected after 24–36 hours. Conversely in the case of viral, gonococcal or Pseudomonas infections the ocular involvement may have a negative effect on visual function and in some cases cause blindness. Further, consequence of accompanying systemic dissemination of these agents may even be fatal.

Prevention

Neonatal conjunctivitis may be prevented by the use of topical prophylaxis in the infant or by prenatal screening, treatment and follow up of infected mothers. The efficacy of maternal screening depends mainly on the incidence of chlamydial and gonorrhoeal carriers, the availability of diagnostic facilities as well as therapy. These measures essentially require an adaptation of infrastructure and resources including a well organized medical system with appropriate antenatal care in order to screen, diagnose and treat sexually transmitted infection in pregnant women. In developing countries this is frequently not possible where the costs must be compared to those of treating infection and complications in the infant itself. In the case of routine prophylaxis use it is advised to treat all newborns including those born by caesarean section in the first hours of birth. Traditionally, this has included the use of 1% silver nitrate ophthalmic solution. However, since this treatment is not successful in all cases and may cause transient chemical conjunctivitis in a high proportion of newborns, erythromycin and tetracycline ophthalmic ointment have also been introduced as prophylactic agents. Recent studies indicate that 2.5% povidone-iodine solution may also be effective in preventing ON causing less chemical conjunctivitis as compared to silver nitrate and erythromycin.

In some developed countries where incidence of ON is very low and no longer poses a public health issue a strategy of early treatment of infected neonates rather than routine prophylaxis has been adopted. In order for this strategy to be effective regular standard follow-up of infants must be ensured. However, it is seen that growing populations, urbanization and increasing promiscuity have caused an increase in the incidence of ON.

Infants born to mothers without adequate prenatal care are the population most at risk for developing ON. Owing to its high association with serious eye and systemic consequences, neonatal conjunctivitis still remains an important public health issue worldwide. Although not universally accepted some countries such as Australia, Sweden, Denmark, Ireland and Great Britain have abandoned the use of routine prophylaxis after birth in favour of screening for STDs and better prenatal care. Consequently, further epidemiological research and monitoring of the incidence of ON and the prevalence of the various agents in different parts of the world are required. With this knowledge preventative and treatment strategy options can be adjusted in accordance to experience with alternative preferences so as to be applicable for broader use.

Conclusion

Although in developed countries neonatal conjunctivitis is not very common it still represents an important public health issue worldwide. Preventing neonatal eye infection by screening and when required treating STDs in pregnant women are possible only in countries where medical care is well organized. General screening requires large financial resources which developing countries cannot sustain and thus eye infection in newborns still represents one of the major health problems in these areas. There is still no optimal agent for efficient prophylaxis of ON whereby the ideal treatment should be highly and equally effective in the prevention of all infectious causes particularly chlamydial and gonococcal, whilst simultaneously being non-toxic. Given that gonococcal ophthalmia presents the greatest risk to visual impairment in newborns, prophylactic and therapeutic procedures should be primarily directed against this type of infection.

In summary, since prophylaxis of ON whilst important is not always effective emphasises the need of all involved in the care of newborn babies to acquire greater knowledge and awareness of differential diagnosis and proper ON treatment strategies. This understanding can subsequently be applied so as to prevent serious visual impairment and blindness that may occur in the case of unrecognized and untreated neonate eye infections.

References

KONJUNKTIVITIS NOVOROĐENČADI

Snježana Kaštelan, Ema Kasun, Željko Štajcer, Boris Kasun

Ključne riječi: konjunktivitis novorođenčadi, etiologija, klinička slika, liječenje, prevencija

ŠAŽETAK. Oftalmija neonatorum (ON) ili konjunktivitis novorođenčadi je akutna serozno-gnojna upala spojnice koja se javlja kod djece tijekom prvih 28 dana života. ON se javlja s prevalencijom od 1,6% do 12%, a u zemljama u razvoju čak i do 23%. Može se podijeliti u neupalne i upalne konjunktivitise. Najčešći neinfektivni uzrok je kemijski konjunktivitis dok infektivni uključuju bakterijske, klamidijske i virusne infekcije s klamidiom kao najčešćim uzrokom. Klinički se ON manifestira gnojnim, serozno-gnojinim ili seroznim sekretom u jednom ili oba oka, podražajem spojnice te oteklom vježom. U nekim slučajevima upala očiju može biti udružena i sa sustavnom infekcijom. Vrijeme pojave konjunktivitis novorođenčadi. Paediatr Drugs 2005;7(2):103–10.


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