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REVIEW

Listeria infections of the eye

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ABSTRACT

The bacterium *Listeria monocytogenes* resides originally in the environment. Infections of the eye have been induced experimentally; for example, in rabbits and guinea pigs. Natural ocular infections occur in various animals; in most instances, they are induced exogenously; for example, by contaminated silage affecting primarily the conjunctiva, cornea, or the anterior chamber. Sporadic infections as well as outbreaks have been described. In humans, besides exogenous infections, endogenous infections also occur, inducing mainly endophthalmitis. Since an exact diagnosis of the causative agent is often delayed, specific therapy starts too late, so that the outcome is often poor. The antibiotics of primary choice would be ampicillin or a quinolone such as moxifloxacin or levofloxacin. The role of fosfomycin for therapy of ocular infections is discussed.

Keywords: Ampicillin, Endophthalmitis, Fosfomycin, Hypopyon, Keratoconjunctivitis, *Listeria monocytogenes*

Introduction

Among the various *Listeria* spp., which are present in the environment especially in soil and various food items including silage, *Listeria monocytogenes* is the most pathogenic species for humans as well as animals. The clinical signs of overt infections are variable. Septicemia and meningoencephalitis are the most frequent and most important manifestations of human infections; in addition, inflammatory manifestations in various solid organs occur (1, 2). Eyes are only rarely affected (1). In principle, 2 different pathogenetic trends occur; namely, exogenous inoculation, resulting in local infection of conjunctiva and cornea, and, on the other hand, endogenous infection, when bacteria cross the blood-eye barrier, resulting in endophthalmitis (3).

Among the pathogens found in bacterial infections of the eye, *L monocytogenes* plays a minor role; about 2%-8% of bacterial endophthalmitis cases may be due to this pathogen (4). In most instances, the *Listeria* infections are misdiagnosed initially, because this entity is unexpected. Hence, specific antibiotic therapy is often delayed and insufficient, leading to complications that may persist after resolution of the initial event.

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Experimental infections

In 1934, Anton tested the pathogenicity of *L monocytogenes* by inoculating the pathogenic bacteria onto the intact conjunctiva of guinea pigs inducing an acute, purulent keratoconjunctivitis (5). Rácz et al (6) studied this model in detail and documented by means of electron microscopic pictures that these bacteria are able to reside and multiply within host cells, which explains some of the particular aspects of the pathogenesis of listeriosis. Zaidman et al (7) inoculated a fresh bacterial isolate from a patient with keratoconjunctivitis into the eye of rabbits. The authors stated that high doses of *L monocytogenes*, namely 10^5 or even 10^7 bacterial cells, were necessary to induce an eye infection within 3 days. An inoculation of *L monocytogenes* into the eyes of 2 sheep also resulted in an acute inflammation (8). Another model has been described (9) using isolated conjunctiva explants obtained from cattle eyes postslaughter. Differences in pathogenicity of various isolates have been described. The susceptibility to lysozyme, which is part of the innate immunity in the tear fluid of a host, plays a certain role. This enzyme is able to attack the peptidoglycan backbone of the cell wall of all Gram-positive bacteria (10).

Infections in animals

Epidemiology

A spontaneous outbreak of listerial keratoconjunctivitis in rabbits was observed in 1956 by Pacheco and Dias (11). Later, such infections were described in sheep (8, 12-15) as well as fallow deer (16). Listerial keratoconjunctivitis is a rather common problem in cattle (9, 12, 17-21). Occasionally, large outbreaks in cattle herds have been observed

(21, 22, 23), especially during wintertime. Hence, *Listeria* infections of the eye are of some importance in agriculture. Infections in horses are less frequent and occur sporadically (21, 24-26).

Signs and symptoms

Keratoconjunctivitis in sheep is a painful disease. It begins with hyperemia, serous lacrimation, increased blinking, and blepharospasm or ptosis. A periorbital edema with chemotic palpebral conjunctivae can be seen. Later, the conjunctival blood vessels become dilated, so that redness develops. The vessels may immigrate into the cornea, which will become opaque. The lesions may remain confined to the cornea itself. Beginning with a stromal edema of the cornea in some instances, the endothelium as well as the Descemet membrane may be damaged during the ongoing infection. When the Descemet membrane is weakened, the intraocular pressure will induce a descemetocele, leading finally to a localized corneal perforation and ulceration (19).

This inflammation, often resulting in corneal defects, may cause temporary visual loss or—in severe cases—even permanent blindness. Often both eyes are affected, although the infection will start mostly in one eye only. In general, animals begin to recover after a week, but sometimes they remain ill for 3-4 weeks with weakness and fever (13).

After 2 to 5 days, the exudate becomes purulent and a pannus spreads all over the cornea. In uncomplicated cases, the pannus subsides and leaves a pigmentation of the cornea in a ring or a band around the rim. Sometimes some sequelae will remain for a while, causing temporary visual loss or—in severe cases—even permanent blindness.

In most instances, the infection remains confined to cornea and conjunctiva. In a few cases, the iris, ciliary body, and uvea were also affected, complicated sometimes by the development of a hypopyon, often dark pigmented (16, 19, 20, 27). It has been assumed that this response is not a consequence of bacterial penetration but rather an overreaction of the immune system of the eye producing iritis as well as stromal keratitis (19). Anterior and posterior synechia of the inflamed iris may persist.

Pathogenesis

Infection results from direct entry of *L monocytogenes* from the exterior into the eye. Exposition occurs during consumption of contaminated silage or haylage (9, 16, 26, 27). *Listeriae* regularly present in soil are able to grow under favorable conditions in hay and silage and in certain islands high numbers can be found. The cows may come into contact their with the bacteria when they burrow into the baled silage with heads (19). The silage eye or new forest eye disease is a familiar term for ocular listeriosis in veterinary medicine. In some cases, however, the proper source of infection may remain obscure, because the silage or the environment have not been examined thoroughly in every case. Furthermore, molecular typing, which has been shown to allow characterization of outbreak strains, revealed that the clone isolated from conjunctival swab was not in every case identical with the isolate from the silage or from the environment. Indeed, multiple clones of *L monocytogenes* are present in the silage and in the surroundings, including those that are not found in infected eyes (21).

Although *L monocytogenes* is able to actively cross anatomic barriers by invasion of epithelial cells (2), in most instances ocular irritation with straw, mineral wool, or sawdust (14) or physical damage to the cornea by feed (19) or by a foreign body (26) will prepare the way for the invasion of *Listeriae*. Indeed, *L monocytogenes* was occasionally isolated from eyes of healthy cows (9, 19), showing that additional predisposing factors may be necessary to start overt disease. The pathogenic bacteria inducing eye infections did not belong to one special clone (21); there is no specific subtype or strain of *L monocytogenes* possessing special ocular tissue tropism but rather many strains of *L monocytogenes* irrespective of serovars dispose of the required virulence factors to induce infections of the eye.

Diagnosis

Microscopic detection of Gram-positive rods in conjunctival swabs gives initial but incomplete evidence. Cultural proof and biochemical characterization is necessary for the final diagnosis of infection with *L monocytogenes*. Serovar determination and molecular typing has been done in some cases to elucidate genetic relationships for explanation of epidemiologic linkages.

The number of living *Listeriae* in a clinical sample may be low, not least because it can be suspected that some bacteria will be hidden intracellularly (26). This means that possibly in some cases of listerial keratoconjunctivitis of animals the diagnosis will be missed. Hence, this infection may be more prevalent than assumed. The modern techniques to identify specific DNA sequences, such as PCR, are possibly more sensitive and can even detect dead bacteria, which would be of special significance after empirical therapeutic attempts.

Therapy

Usually the infection in animals is benign, so that they recover spontaneously after a week or so (8, 13, 16, 18, 19). In rabbits experimentally infected with high doses of *L monocytogenes*, the infection waned after 4 weeks without any antibiotic treatment (7). In case of persistent infections, therapy started mostly by topical application of ophthalmic ointments or eyedrops. Corticosteroids have been added to reduce the excessive inflammatory as well as immune response and to prevent corneal clouding and persisting scarring and possibly uveitis. Diclofenac eyedrops also will be able to reduce the inflammatory reaction (26).

Various antibiotics, for example penicillin, chloramphenicol, gentamicin, fusidic acid, tetracyclines, and quinolones, have been used. Resistance of *L monocytogenes* to any of these antibiotics is extremely rare (28-31). (Inherent resistance of *L monocytogenes* to polymyxin B, which has been used for calculated topical treatment of bacterial eye infections, exists.) In experimental infections, local application of penicillin was as effective as gentamicin, but the combination was superior (7). In naturally infected animals, failure of locally administered antibiotics has been observed often.

Most likely this has been due to the fact that *L monocytogenes* is an intracellular bacterium and few antibiotics are able to eliminate these hidden pathogens (28). This may also be the reason for recurrences, which happen rather commonly (21).

Hence, effective treatment protocols often include concomitant use of topical and parenteral antibiotics such as penicillin and ampicillin (21, 26). This is difficult to understand, because these β-lactam antibiotics do not achieve high concentrations in tear fluid (32) and do not penetrate well into host cells (28). Theoretically, quinolones (especially moxifloxacin) should be more efficient for the treatment of *Listeria* infections of the eye because they are endowed with some advantages. They are highly active in vitro against *L monocytogenes*. They are efficiently secreted into tissue fluids so that even higher concentrations are achieved there than in serum. Furthermore, they penetrate well into host cells and have access to intracellular sites, especially the cytoplasm where *L monocytogenes* is residing and multiplying (28, 33).

Conclusion

Listeria infections of the eye are frequent in sheep and cattle when they are exposed to contaminated silage or haylage. At least in some instances, mechanical damage may facilitate the entry of bacteria into the cornea or conjunctiva. It seems that generally the bacteria remain confined to the superficial layers. A heavy local inflammatory response also may affect the adjacent structures of the anterior chambers of the eye, so that besides keratitis and conjunctivitis, iritis und uveitis also can develop. Although spontaneous cure may occur, local and often systemic antibiotic therapy is required in most instances. An optimal regimen cannot be named. Long-lasting or recurrent infections are occasionally seen in spite of rational therapy.

Infections in humans

Eye infections of humans with *Listeriae* are much less frequent than of animals and occur sporadically (1). In principle, 2 different courses of the disease have been described in humans; namely a local keratoconjunctivitis of more or less immunocompetent individuals as well as an endophthalmitis or a chorioretinitis, respectively, complicating a disseminated listeriosis in immunocompromised patients.

Exogenous infections inducing keratoconjunctivitis

Case report

A 16-year-old boy without any predisposing diseases developed an ulcerating keratitis accompanied by a mild conjunctivitis of the left eye exclusively. He had assisted his father regularly in the cowshed of their farm, where he presumably acquired the pathogens from silage. *Listeria monocytogenes* serovar 1 was isolated from conjunctival swabs 2 weeks after beginning of symptoms. In spite of long-lasting local therapy with antibiotics (the precise regimen of the antibiotics used was not documented in the patient record), he did not recover immediately, but only after 6 weeks. Because of serious visual loss due to corneal defects, a keratoplastic replacement of the cornea was necessary.

Reports in the literature

In husbandry, not only animals but also farmers are exposed to *L monocytogenes* in silage or in other often not identified sources in the environment. Listerial keratoconjunctivitis in farmers has been reported occasionally. Sometimes a foreign body in the cornea was accused to have facilitated the invasion (34). Zaidman et al (7) reported a keratoconjunctival infection in a 39-year-old man after he handled infected animals. Furthermore, it has been discussed that a treatment with corticosteroid eyedrops could have facilitated the onset. The therapy with corticosteroids had been continued in this patient after the beginning of overt infection, since a delayed diagnosis of listerial infection has been made. The unusual complication, namely the formation of a limbal abscess, was considered as a consequence of the compromised local defense due to corticosteroids.

Exposure to *L monocytogenes* may occur not only in agricultural environments but also in urban situations. There is an anecdotal report of ulcerative keratitis in a patient using contact lenses (35). Various food items, such as lettuce, soft cheese, salami, and graved salmon, can be contaminated (2) and presumably may be the sources of eye infections by lubrication when hand hygiene is neglected. A 49-year-old woman without any debilitating disease living in a large Swiss city and working in an office of the governmental administration developed keratitis due to *L monocytogenes* without any contact with animals; a source could not be identified. It has been argued that this case of ocular manifestation could be part of the epidemic of more than 40 cases of systemic listeriosis in the region during that period (36). In an 85-year-old diabetic woman without any contact with animals and no previous ocular disease, a necrotizing ring ulcer of the cornea with hypopyon was diagnosed. An inciting injury was not reported. The only predisposing factor was diabetes (37). Tay et al (38) reported on sclerokeratitis with hypopyon in a 25-year-old rugby player. Various viral and fungal reasons of the infection were discussed, but the proper causative agent, *L monocytogenes*, was detected only after about 2 months. The proper source of infection could not be discovered.

In general, local infection remains confined to the anterior portions of the eye (39). In one report, however, eye infection with *Listeria* started with conjunctivitis and resulted finally in endophthalmitis (40). Recurrent heavy inflammatory reactions of the conjunctiva and the anterior chamber were observed after unilateral *Listeria* infection of the eye in an otherwise immunocompetent patient (41).

Signs and symptoms

Exogenous infections in immunocompetent individuals affect primarily the anterior portions of one of the eyes. Inflammation of the conjunctiva and cornea are often combined. In severe cases, the anterior chamber of the eye is afflicted, so that a hypopyon typically develops. This complication may be due to a heavy immune reaction leading to elevated levels of inflammatory mediators (41).

Endogenous infections

Systemic listeriosis due to contaminated food items occurs mainly in immunocompromised or in aged people. However, systemic listeriosis occasionally occurs in persons without any obvious risk factors (2).

During septicemia, the bacteria may spread predominantly into meninges and brain but also into various organs, including the eye. Sporadic cases of listerial ocular infections have been reported in patients with sepsis or meningitis (3, 4, 42-49). One case was associated with an outbreak of listeriosis due to contaminated cantaloupe from a single farm (50). Of special interest is a report on a fatal outcome of endophthalmitis in a young female patient with rheumatic arthritis treated with tumor necrosis factor-α inhibitors (51). By chance, it may happen that both eyes are infected (52).

Microscopic evidence of Gram-positive rods in conjunctival swabs, corneal scrapings, anterior chamber taps, or vitreous biopsies is rapid and can be a first hint. The final diagnosis is confirmed by cultural isolation of the pathogen after 1 or 2 days. A more rapid diagnosis can be achieved by molecular biology (53).

Septicemia during systemic listeriosis may be short-lived and the patient will experience a flu-like episode only (2). Therefore, in a few cases the eye can be the only manifestation of a presumably hematogenous distribution without any identified extraocular septic foci (4, 39, 53-59). If this happens in patients with no underlying disease or state of immunosuppression (54, 60), it will finally remain obscure in practice whether the eye was involved during an endogenous or an exogenous mode of infection (41).

Signs and symptoms

In principle, endogenous bacterial infections may be represented as anterior, posterior, or panophthalmitis (47). In the majority of cases, the beginning is protracted and the development is slow, but one has to bear in mind that fulminant courses are possible (49, 61). The severity of symptoms and complaints is variable depending on the physical condition of the patient and on the time of onset of specific antibiotic treatment. Occasionally there is a good visual outcome (48). Often listerial endophthalmitis may be a devastating disease. Because physicians are not aware of the role of *L monocytogenes* as a cause of eye infections, this particular entity is often misdiagnosed (3) or the time to final diagnosis is often prolonged (38). Numerous reports show poor visual outcome of *Listeria* infections of the eye; final vision is often worse than 2/200 (3, 8, 41, 56). Corneal scars, cataract formation, persisting synechia, vitreous opacities, as well as retinal scars may demand surgical interventions in many cases, such as keratoplastic repair (38), pars plana vitrectomy (50), or even enucleation of the eye, especially when the antibiotics used, for example, cephalosporins, are not adequate for *L monocytogenes* (37, 61).

Antibiotic therapy

Usually, keratitis and conjunctivitis are treated topically with eyedrops and ointments. Corticosteroids may help to suppress the inflammatory response, to reduce acute redness, pain, blepharospasm, lacrimation, and purulence. However, bacterial propagation may be supported by blocking of defense mechanisms by these immunosuppressive agents. Since *Listeria* infections of the eye are rare and the exact diagnosis will be in most instances available after a considerable delay, it may happen that antibiotics are used that are a priori inactive against *L monocytogenes*, i.e., cefazolin and polymyxin. On the other hand, aminoglycosides, such as neomycin, gentamicin, or amikacin, should theoretically be active, as well as penicillin derivatives, especially ampicillin, macrolides, such as erythromycin, tetracyclines, and quinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, whereby moxifloxacin exerts the best bactericidal effect against Gram-positive bacteria and against *L monocytogenes* in particular (30, 31). The clinical experience is disappointing, however (7, 34, 40). First, this may be due to the fact that the diffusion of antibiotics into the tissue layers where the bacteria reside was insufficient. Second, *L monocytogenes* is a facultative intracellular pathogen. Although a large part of the bacteria resides extracellularly (26, 37), a certain, considerable part of the bacteria may grow inside host cells, where they are protected from those antibiotics that do not act at this site (33).

Occasionally, subconjunctival injections of antibiotics have given beneficial effects (47).

In general, however, systemic therapy in combination with topical delivery is necessary to achieve a reasonably satisfactory result of keratitis and conjunctivitis.

Endogenous infections inducing endophthalmitis or panophthalmitis require more than external antibiotics; namely, intravitreal application of appropriate antibiotics and systemic antibiotic treatment as well.

Intravitreal instillation of antibiotics has been attempted with various antibiotics (55, 61). This therapeutic approach has several fundamental limitations: the volume of drug solution that can be injected is rather small, namely 0.1 mL or maximally 0.2 mL, and consequently the amount of drug instilled is low. The stability of some antibiotics, especially of the penicillin derivatives, is restricted but multiple injections are difficult to realize for practical reasons. The diffusion of antibiotics from the vitreous cavity into the adjacent structures is poor. Therefore, few antibiotics are suited for this procedure. Repeated intravitreal injections of vancomycin (1 mg/0.1 mL) and irrigation of the anterior chamber with this antibiotic proved to be helpful (4, 40, 48). In summary, this measure can be only complementary.

Several antibiotic regimens have been used for systemic treatment of listerial eye infections. The first choice is IV ampicillin (for example, 4 2-3 g per day for at least 14 days) (29, 33). Other regimens, for example, penicillin (40), also have been applied successfully. The combination of a penicillin derivative with gentamicin is often recommended, because in vitro these antibiotics act synergistically. There is no proof, however, that the combination has better clinical outcome than ampicillin alone (30). Furthermore, the concentrations of aminoglycosides in the various compartments of the eye are low after IV application (44). Quinolones also have been used with certain therapeutic benefit (4). These antibiotics, especially moxifloxacin, encompass a broad spectrum of bacterial pathogens causing eye infections including *L monocytogenes*. They are outstanding because of their good antimicrobial competence, i.e., low minimum inhibitory concentrations, bactericidal activity (30), and potency against intracellular bacteria (33). Since they achieve therapeutic levels in the noninflamed eye after oral (62) as well as after topical application (63), they may represent a major advance for managing anterior and posterior segment infections of the eye. The therapeutic success of topical, local, and systemic antibiotics is not convincing in all cases, however. In any case, one has to anticipate that definite sequelae may remain, especially when antibiotic treatment active against *L monocytogenes* is started with delay (41).

Theoretically, it could be expected that the use of fosfomycin could eventually complement and improve the therapeutic effect of other antibiotics, in particular ampicillin, which remains the drug of choice for the therapy of *Listeria* infections (30). First, this tiny molecule diffuses easily across anatomical barriers and penetrates well into the various compartments of the eye. The intravenous administration of 4 grams every 8 hours leads to high intraocular levels (64, 65). In general, even higher doses, namely 8 grams every 8 hours, are used for treatment of severe infections (66). Second, this small molecule passes membranes of host cells and it is accumulated intracellularly (33, 67), hence it is active against intracellular *L monocytogenes* (30, 33). This is a paradox, because this antibiotic is generally inactive against *L monocytogenes* in vitro, where the antimicrobial activity is tested under high concentrations of glucose-6-phosphate (68). The explanation is that under such intracellular conditions, when the concentration of glucose is low, the bacteria have to activate glucose-6 phosphate inward transport systems, and these influx pumps will transport fosfomycin. It could even be speculated that fosfomycin also might be active on extracellular *L monocytogenes* in the eye cavity, because the glucose level in the vitreous fluid is definitely lower than in serum (69). Moreover, it can be expected that in inflamed tissue, the glucose levels are further reduced.

Discussion

Listeria infections of the eye have been induced experimentally in several animal models. Natural infections of the eye have also been described in various animals. Usually conjunctivitis and keratitis develop after exposure of the eye to *Listeriae* in contaminated silage or haylage. The heavy inflammatory reaction may also affect the anterior chamber of the eye. The incidence of human infections of the eye with *L monocytogenes* is low, although it can be anticipated that some cases have failed to be diagnosed correctly. Several case reports have been published, which are summarized here. In principle, there are 2 different manifestations, namely infections of the anterior portions, which occur by accidental external inoculation of the pathogens in otherwise healthy subjects, and endophthalmitis in varying degrees, occurring mainly in frail, immunocompromised patients with systemic listeriosis such as septicemia and/or meningitis or encephalitis, respectively. Often, serious sequelae, at least a remarkable visual loss, will persist even after rational therapy, especially when the exact cause of infections is diagnosed with delay. In most cases, topical, intraocular, as well as systemic antibiotics are necessary. Although *L monocytogenes* is susceptible to most of the common antimicrobials, they may survive a therapeutic attack and persist, since they are able to reside and multiply within various host cells, i.e., phagocytic cells, stromal cells, as well as epithelial cells, where they stay protected from most antibiotics. Theoretically, moxifloxacin seems to be well-suited for therapy of *Listeria* infections of the eye, because of its excellent direct antimicrobial activity and its suitable pharmacologic properties achieving therapeutic levels in the eye after topical as well as oral application. Reduction of the inflammatory response by corticosteroids may be beneficial.

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