OPHTHALMIC MANIFESTATIONS IN LYME BORRELIOSIS

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ABSTRACT

Lyme Borreliosis is a multisystem disorder caused by the spirochete *Borrelia burgdorferi*. Although many ocular manifestations have been attributed to Lyme Borreliosis, they remain a rare clinical feature of the disease. The spirochetes invade the eye early and remain dormant, accounting for both early and late ocular manifestations which range from conjunctivitis and keratitis to intraocular inflammatory syndromes and neuro-ophthalmic manifestations. Especially in endemic areas, ophthalmologists need to be aware of *Borrelia burgdorferi* as a possible causal agent. The aim of this article is to present a short review of ophthalmic disorders resulting from *Borrelia burgdorferi* infections.

KEY WORDS

Borrelia burgdorferi, Lyme Borreliosis, eye, ophthalmic manifestations

INTRODUCTION

There has been a growing awareness of Lyme Borreliosis (LB) during recent years. *Borrelia burgdorferi* (*Bb*) infection can be associated with a variety of signs and symptoms including neurologic, dermatologic, cardiac and ophthalmic disorders. The infectious agent causing LB is the spirochete *Bb* which is transmitted by ixodid ticks (1,2). Recently, *Bb* has also been found in mosquitoes and deer flies (3).

The clinical course of LB is divided into three stages (4,5). Stage I directly follows the bite by an infected tick. Patients develop a typical skin lesion, erythema migrans (EM) (6) and, in some cases, non-specific influenza-like symptoms and fever. After several weeks, spirochetes spread throughout the body and patients may develop neurological, skin and cardiac manifestations (Stage II) (4,7-9). Stage III is mainly characterized by polyarthritis, progressive encephalomyelitis similar to multiple sclerosis (4,5,8) and skin disorders with acrodermatitis chronica atrophicans (10). However, not every patient follows this course (6,11,12). In fact, no clear line can be drawn between the three stages, neither with respect to time of occurrence nor to symptoms.

Bb has been isolated from blood, cerebrospinal fluid and various tissues (7,13). Although *Borrelia* has also been identified histologically in the iris, the retina and in the vitreous humour (14-19), little attention has been focused on the ophthalmic manifestations of LB. Since LB can be associated with a number of ophthalmic manifestations, *Bb* should be considered as a possible causal agent. However, strict criteria should be applied to avoid

overdiagnosis. The aim of this article is to review the reported ophthalmic disorders associated with *Bb* infection.

OPHTHALMIC MANIFESTATIONS OF BORRELIA BURGDORFERI INFECTION

1. OPHTHALMIC MANIFESTATIONS IN STAGE I (SEE TABLE 1)

1.1. Conjunctivitis, periorbital edema (5,13,18,20,21) Follicular conjunctivitis with photophobia and periorbital edema have been observed in 10% of patients in the early stages of LB.

2. OPHTHALMIC MANIFESTATIONS IN STAGE II (SEE TABLE 1)

2.1. UVEITIS

2.1.1. Iridocyclitis (5,17-20, 22-37): Several case reports of LB and granulomatous iritis with posterior synechia have been published. Kauffmann and Wormser showed that panuveitis with disseminated chorioretinitis may follow iridocyclitis (19).

2.1.2. Pars planitis (25,27,28,31,35,38-40): Chronic intermediate uveitis with classic snowbanking and severe cystoid macular edema was reported by Breeveld et al. (38). In spite of the fact that the patient had suffered for 10 years, the ocular symptoms responded promptly to intravenous antibiotic therapy. Another case of pars planitis associated with facial palsy was presented by Winward et al. (35).

2.1.3. Vitritis (15,22,27,28,35,38,41-43): Several case reports of vitritis have been described. In 1991 Rothova et al. reported a case of spiderweb vitritis in the Lancet (43). Although it is only one single case report, it demonstrates the variety of ophthalmic manifestations of LB. Kuiper et al. observed vitritis in association with Lyme meningitis and cranial polyneuritis 6 weeks after a tick bite causing EM (42). Winward et al. described several patients with positive laboratory findings of borreliosis who had recurrent bilateral vitritis and granulomatous iridocyclitis relatively resistant to therapy (35).

2.1.4. Chorioretinitis (5,15,22,31,44,45): Two cases of bilateral diffuse chorioiditis, cystoid macular edema and exsudative retinal detachment have been described. These patients also suffered from lymhocytic meningitis secondary to LB. The dramatic improvement of ocular complaints in these patients after doxycycline therapy suggests LB as a possible cause.

2.1.5. Pigmentepitheliitis (16,33,46,47): Bialasiewicz et al. observed a patient with hyper- and depigmentations in the macular region in association with *Bb* seroconversion (46). It was similar to pigmentepitheliitis. Recently, Wiegand described cases of presumed acute multifocal posterior placoid pigmentepitheliopathy in association with LB (33,47). Further investigations need to prove the relevance of this coincidence.

2.1.6. Retinal vasculitis (5,22,28,31,37,48): Several cases of retinal vasculitis in LB associated with vitritis and pars planitis have been presented. One patient with positive *Bb* serology developed retinal neovascularization and cystoid macular edema. He received oral tetracycline therapy and showed marked improvement. In two other cases of severe retinal vasculitis associated with *Bb* infection, surgical therapy was applied after antibiotic treatment was unsuccessful (28). Retinal vasculitis can be expected to occur in LB as similar findings are frequently seen in the later stages of syphilis, another spirochetal infection (28).

2.2. Endophthalmitis (17,19)
Kauffmann et al. described a patient who showed severe unilateral panendophthalmitis following an insect bite causing EM (19). A lensectomy and vitrectomy were performed; Lyme spirochetes were found in the vitreous specimens.

2.3. Neuro-ophthalmic manifestations

2.3.1. Optic neuropathy

2.3.1.1. Optic neuritis (5,8,16,18,22,24,29,31,35,49-51): To date, there are only a few reports of optic neuritis associated with LB. Winward et al. observed a case of bilateral optic neuritis and mild vitritis (35). In these patients, central scotoma and afferent pupillary defect were present as well as other neurologic manifestations.

2.3.1.2. Anterior ischemic optic neuropathy (32,34, 52,53): A case of ischemic optic neuropathy secondary to LB with an inferior altitudinal field defect was reported by Schechter et al. (53). Pizzarello et al. described another case of ischemic neuropathy following a tick bite causing EM (52). Temporal artery specimens showed the typical appearance of giant cell arteritis, but a silver stain suggested spirochetes within the multinucleated giant cells. Ceftriaxone therapy led to a marked improvement of visual acuity.

2.3.1.3. Optic atrophy (11,18,20,25,34,48,54,55): Optic

Table I. Ophthalmic manifestations of Lyme Borreliosis by stage.

Ocular symptoms	Systemic symptoms	Routine serology
Stage I (4-8 weeks)		
conjunctivitis	primary affect	IgG negative
periorbital edema	erythema migrans	IgM negative
photophobia	lymphadenosis cutis benigna	
	generalization	
	fever, malaise, cephalea	
Stage II (< 1 year)		
uveitis	organic manifestations	IgG increasing
iridocyclitis	dermatologic	IgM high
pars planitis	multiple erythemata	
vitritis	neurologic	
chorioretinitis	meningitis	
pigmentepithelitis	radiculoneuritis	
AMPPPE*	cranial neuritis	
retinal vasculitis	cardiac	
endophthalmitis	myocarditis	
neuro-ophthalmic manifestations	pericarditis	
optic neuropathy	artrioventricular block	
optic neuritis	rheumatologic	
ischemic neuropathy	mono-, oligoarthritis	
optic atrophy		
papilledema		
pseudotumor cerebri		
Leber's neuroretinitis		
cranial nerve palsy		
oculomotor palsy (III, IV, VI)		
facial nerve palsy		
pupillary disorders		
Argyll Robertson pupil		
Horner's Syndrome		
paralytic mydriasis		
Stage III (> 1 year)		
keratitis	organic manifestations	IgG high
interstitial keratitis	dermatologic	IgM low
peripheral ulcerative keratitis	acrodermatitis chronica atrophicans	
episcleritis	neurologic	
myositis	progressive encephalomyelitis	
neuro-ophthalmic manifestations	rheumatologic	
optic neuritis	oligo-, polyarthritis	
ocular nerve palsies	chronic erosive arthritis	
visual field defects		
nystagmus		

*AMPPPE = acute multifocal posterior placoid pigmentepitheliopathy

neuritis, ischemic neuropathy and chronic papilledema in pseudotumor cerebri may each be responsible for optic disc atrophy in patients with chronic LB. Bertuch et al. described a case of progressive optic disc pallor following a presumed diagnosis of LB without previously observed optic nerve disorders (55).

2.3.1.4. Papilledema (5,11,18-20,27,35,37,39,48,49,51,56-58): Optic disc edema may result from various causes. Only a minority of patients with Lyme meningitis develop disc edema. The latter leads to blurred vision and is usually not associated with elevated intracranial pressure (39). Optic perineuritis (11,18,19,57) is probably the reason for disc swelling in the cases described by Kauffmann et al. and Reik et al. (11,19). LB associated pseudotumor cerebri with increased cerebrospinal fluid pressure has been reported in several cases (35,49,56-58).

2.3.1.5. Leber's stellate neuroretinitis (5,20,48,49,59,60): This disorder is caused by vasculitis of the optic nerve head, causing distinct disc edema, venous congestion and star-shaped lipoid exudation. It has been reported in viral diseases and neurolues. Recently, a few cases of Leber's stellate neurretinitis in LB have also been observed (59).

2.3.2. CRANIAL NEUROPATHY

2.3.2.1. Facial nerve palsy (8,11,27,28,35,49,51,54,56,61-65): Facial nerve palsy, occasionally associated with exposure keratitis, is the most common cranial neuropathy occurring in approximately 50% of patients with Lyme meningitis. Sometimes it is the only manifestation of the disease, although multiple recurrences have also been observed (35).

2.3.2.2. Oculomotor palsy (8,9,11,24,30,31,35,42,49, 51,62,63,66,67): Cranial neuropathy with oculomotor, trochlear and abducens nerve palsies have been reported. Diplopia is the typical ocular complaint in this case. These palsies may occur individually or in combination with other neurologic abnormalities. LB has been reported in children suffering from late onset strabismus and diplopia (31,66).

2.3.3. Pupillary disorders (11,22,68)

In the literature, there are only anecdotal reports about the association of pupillary dysfunction and LB. Argyll-Robertson pupil was described in Reik's report in 1986 (11). This disorder is also common in neurolues. A case with reversible Horner's Syndrome was observed by Glauser et al. (68). Karma et al. reported a case of bilateral paralytic mydriasis (22).

3. OPHTHALMIC MANIFESTATIONS IN STAGE III (SEE TABLE 1)

3.1. CONJUNCTIVITIS AND EPISCLERITIS (51,69-71)

Zaidman observed a case of chronic LB with tarsoconjunctival scarring, symblepharon and episcleritis (71). These manifestations are common in autoimmunological eye diseases. Thus, an immune-pathogenesis can also be considered in this case of late LB.

3.2. KERATITIS

3.2.1. Interstitial keratitis (5,19,31,49,55,69,70,72-77): Interstitial keratitis in chronic spirochetal infections (*Treponema pallidum*) is well known. In LB, several cases with scattered hazy infiltrates of the deep and superficial stroma have been observed. Only one patient, however, exhibited corneal neovascularization unlike the typical syphilitic keratitis parenchymatosa with early stromal vascularization (19,74). It is interesting to note that these cases of Lyme-associated interstitial keratitis responded to local steroids but not to antibiotic therapy, thus suggesting an immunpathologic origin (74).

3.2.2. Peripheral ulcerative keratitis: A patient with peripheral ulceration secondary to LB was presented (78). It should be mentioned that this manifestation is commonly seen in autoimmune diseases.

3.3. ORBITAL MYOSITIS (79)

A single case of orbital myositis was described in the literature: a five year-old girl with typical manifestations of late LB. This child developed unilateral orbital pain, proptosis and diplopia. Computerized tomography disclosed myositis of the medial and inferior rectus muscle and haziness of the retrobulbar fat. Complete resolution was seen after corticoid therapy.

3.4. NEURO-OPHTHALMIC MANIFESTATIONS

The typical CNS manifestation in chronic LB is a progressive encephalomyelitis with fatigue, dementia, multiple cranial nerve palsies as well as cerebellary and extrapyramidal defects and recurrent strokes (80). These disorders are thought to be caused by occlusive cerebral vasculitis (5). MRI scanning shows multiple paraventricular and subcortical demyelinating lesions (5,11,16,18,48,49) similar to those seen in multiple sclerosis. Ocular symptoms in progressive encephalitis

are visual field defects, diplopia and/or nystagmus depending on the site of the cerebral lesions.

CONCLUSION

Ophthalmic manifestations of LB are common and can mimic features of other systemic disorders. A variety of ocular disorders can be found in each stage of LB. The growing awareness of *Bb* infections has certainly contributed to improved diagnosis, but there are still diagnostic difficulties. Especially in cases with uveitis, optic neuritis or oculomotor nerve palsies, it is necessary to consider *Bb* as a possible causal agent (35). It is advisable to investigate the possible history of tick bites, EM and diseases such as arthritis. However, 30% - 40% of cases may show no history of tick bites. Serological tests for *Bb* antibodies can be helpful to support the clinical diagnosis of LB, but one must be aware of the fact that, in endemic areas, positive IgG titres may be an occasional coincidence. On the other hand, a negative result does not necessarily exclude the diagnosis in any clinical situation. Depending on the test used, LB may be seronegative in up to 50% (34,81). In cases with neuro-ophthalmic involvement, an examination of the CSF is recommended (66). In some cases of severe intraocular inflammation, a vitreous tap is required for diagnosis (20), however, it is difficult to prove *Bb* infection histologically. Rigorous criteria should be applied in order to avoid an overdiagnosis of the ocular manifestations of LB (30). The U.S. Centers for Disease Control proposed the definition of LB, as shown in Table 2 (30).

The postulated pathophysiologic mechanism of the disease is the direct bacterial invasion of the tissue and subsequent immunologic reactions resulting in vascular occlusions in chronic stages of the disease (7,31,74). *Bb* has been cultured from blood, cerebrospinal fluid and directly from brain parenchyma (7,13,49), but it has also been identified histologically in the iris, the retina and in the vitreous humour (14-19). The immunlogical reactions which are believed to play a predominant role in chronic LB (31,74), however, have not been elucidated in detail as of yet.

In early LB oral antibiotic therapy shortens the duration of systemic symptoms and prevents the development of delayed disease in most patients. The specific recommendations for antibiotic therapy have changed over the past few years, but treatment failures have occurred with every regimen. Oral tetracycline or penicillin are the current recommended drugs for Stage I of LB. In later stages parenteral antibiotics, such as penicillin or cephalosporins, are required (12,18,30,34). The use of cortiocosteroids in chronic LB is controversial. Steroids apparently have been helpful in treating keratitis, myositis and certain neurologic symptoms in Stage III of LB (12,55,74,76,79). However, caution should always be taken when using steroids in LB, since they may cause severe exacerbation of all the clinical symptoms. Once *Bb* infection is diagnosed, steroids should only be used together with high doses of intravenous antibiotics, even in the late stages of LB.

The increasing number of reports of Lyme associated ocular disorders should alert ophthalmologists to consider *Bb* as a possible causal agent. Serologic investigations for Lyme antibodies are recommended in cases with ocular inflammatory diseases, optic neuropathies and cranial nerve palsies. In complex cases interdisciplinary cooperation with neurologists and infectious disease specialists is crucial.

Table II. Diagnostic criteria for Lyme Borreliosis according to the U.S. Centers for Disease Control (30).

Area	Criteria
endemic	1. Erythema migrans with exposure not more than 30 days prior to onset 2. Involvement of one organ system* and positive antibody test
nonendemic	1. Erythema migrans with positive antibody test 2. Erythema mirgans with involvement of two organ systems*

* musculoskeletal, neurologic, cardiac

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