Borrelia Ocular Infection: A Case Report and a Systematic Review of Published Cases

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Keywords

Borrelia spirochetes · Inflammation/uveitis · Ocular tissue · Polymerase chain reaction · Microscopy

Abstract

Introduction: Lyme borreliosis can cause many diverse manifestations, also ocular disease where the diagnosis of ocular borreliosis is challenging. The primary aim was to report on the evidence of *Borrelia spirochetes* in the ocular tissue in presumed ocular borreliosis. **Methods:** A systematic review of pathological eye conditions was performed where *Borrelia* has been suspected in relevant ocular tissue, together with a case report of diagnosed uveitis with polymerase chain reaction (PCR)-confirmed *Borrelia afzelii* in the vitreous. The evidence for clinical and laboratory diagnosis was evaluated systematically. As a secondary aim, the treatment of ocular *Borrelia* infection was also evaluated for confirmed cases. **Results:** Thirteen includable studies were found, and after the removal of case duplicates, eleven unique cases were extracted. Apart from the present case report, 4 other cases reported strong evidence for the detection of *B. spirochetes* in ocular tissue. Four cases presented reasonable evidence

for assumed detected *Borrelia*, while three additional cases showed only weak diagnostic credibility that *Borrelia* was detected. **Conclusion:** This systematic review, including all reported cases and our case report, supports evidence of ocular infection of *Borrelia* species. Furthermore, in case of suspicion of infection and seronegativity, it is justified to look for *Borrelia* in eye tissue samples. In addition, microscopy without using PCR is not sufficient to confirm the diagnosis of borreliosis on ocular tissue. In the articles studied, there was no unambiguous recommendation of treatment.

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Introduction

Lyme borreliosis, or Lyme disease, caused by *Borrelia spirochetes*, usually transmitted to humans by ticks in the temperate climates, can cause many diverse manifestations, especially in the early stages, before a serological response has developed, establishing that the diagnosis may be complex. Not least, the diagnosis of ocular borreliosis can be challenging. The diagnostic possibilities

provided by serology and clinical findings are limited, and biopsies of eye tissue are seldom without risk. Antibiotic treatment attempts of presumed eye disease caused by *Borrelia* species (spp.) are often arduous and not always of clear benefit. In the differential diagnosis of uveitis, the awareness of these difficulties can lead to a lowered interest in confirming *Borrelia* as a possible genesis.

In the French guidelines of 2019 for Lyme disease, ophthalmological manifestations were given evidence grade B by Gocko et al. [1]. This was motivated by most reports of ocular borreliosis being based only on serological findings, which cannot guarantee *Borrelia* as the cause of the eye condition. The French guidelines referred only to one case of *B. spirochetes* detected in eye tissue reported by Dietrich et al. [2], and two reports of ophthalmological manifestations (uveitis) concomitant to Lyme neuroborreliosis, confirmed by cerebrospinal fluid (CSF) analysis. The French authors concluded that the evidence of ocular *Borrelia* infection is weak. In our current article, we have performed a systematic review of the literature and methodology for a series of those already published cases to assess the evidence that support an ocular infection of *Borrelia* spp. We also present our case of uveitis with polymerase chain reaction (PCR)-verified *Borrelia afzelii* in the vitreous, which was the incentive for this review.

Case Presentation

The patient was a 51-year-old man with mild diet-treated diabetes, otherwise healthy and fit, spending a lot of time outdoors. In September 2016, he was examined because of a one-day history of floaters in the left eye (LE). His best-corrected visual acuity (BCVA) was in decimal Snellen 1.0 in the right eye (RE) and 0.7 in the LE. He was diagnosed as having vitreous detachment. At this time, he had a possible frozen shoulder and itchy skin rash on the abdomen. Two months later, he had metamorphopsia in the LE, and another month later, BCVA was reduced to 0.4. At the examination, both eyes were white with no inflammatory signs in the RE. In the LE, there were small keratic precipitates, 2+ cells in the anterior chamber, a lot of cells and cell aggregates in the vitreous, and a macular epiretinal membrane but no signs of inflammatory retinal changes. He was given 30 mg of oral prednisolone with a good effect on the vitreous cells, and BCVA was 1.0 after one week. C-reactive protein, hemoglobin, platelet count test, white blood cell count, serum ionized calcium, and computed tomography of the chest were normal. Prednisolone was withdrawn and an intravitreal implant of 700 mg dexamethasone (Ozurdex®) was given, in spite of the fact that the patient was not assessed for associated diseases. Three months later, in March 2017, his BCVA decreased to 0.7 in the LE, and there were again cells in the anterior chamber and vitreous, but this time some retinal hemorrhages and multiple white dots in the inferior part of the retina were observed. Further

investigation showed normal values of s-angiotensin-converting enzyme, syphilis serology, serum antineutrophil cytoplasmic antibodies, plasma (P)-immunoglobulin (Ig) A, P-IgG, P-IgM, P-orosomucoid, P-albumin, and P-haptoglobin. *Borrelia* serology was IgG-positive (≥ 200 RU/mL), IgM 21 RU/mL (< 16 RU/mL = no detection; 16–21 RU/mL = borderline; and > 21 RU/mL = detection). He had no history of a tick bite (TB) or erythema migrans (EM). He was given another Ozurdex® and also a 10-day course of oral doxycycline 200 mg per day.

During the following year, another three Ozurdex® injections were given, each with an effect of about three months. In March 2018, a new evaluation was performed with the same level of *Borrelia* antibodies as a year earlier and other blood tests were normal. Fluorescein angiography of the retina and magnetic resonance tomography of the brain were normal. Another identical course of oral doxycycline was given.

In May, a cataract extraction was performed successfully, and in September 2018, a vitrectomy was performed mainly for diagnostic purposes. The vitreous was sent for laboratory diagnostics. Flow cytometry of the vitreous cells showed reactive T lymphocytes with a CD4/CD8 ratio of 1.4 and a normal expression of CD5. There were no B cells or granulocytes and no suspicion of lymphoma. With PCR, there was no detection of adenovirus, herpes simplex virus 1, herpes simplex virus 2, varicella-zoster, or cytomegalovirus DNA. However, 16S rRNA PCR was positive, where the following sequence analysis showed complete homology with *B. afzelii*. The PCR analysis was performed as part of routine diagnostics at the Department of Clinical Microbiology, Karolinska University Hospital, which is under the regulation of the Swedish Board for Accreditation and Conformity Assessment, Swedac. At the time of vitrectomy, a new *Borrelia* serology showed positive titers for IgG (180 RU/mL) and IgM (24 RU/mL).

A two-week course of intravenous ceftriaxone 2 g per day was given. At follow-up, there was an epiretinal membrane with discrete edema which was later resolved with a course of topical corticosteroids and nepafenac. There have been occasional cells in the anterior chamber. The topical treatment was postponed in August 2019. In January 2020, the eye was quiet without cells or macular edema, and the VA was 1.0. In June 2020, the eye had only a few cells in the anterior chamber and the vitreous, BCVA was 1.0 LE, and a parafoveal intraretinal cyst was noticed. A low dose of topical steroids was reinstituted which dried up macula and has kept the vitreous and anterior chamber free, or nearly free of inflammatory cells, and the last visit was on the twentieth of July 2021. There were never any signs of uveitis on the RE.

Methods

Study Selection and Used Criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines [3]. Review protocols were developed accordingly, both for the search and the review process (online suppl. material 1, 2; see www.karger.com/doi/10.1159/000521307 for all online suppl. material). The systematic review at PubMed was conducted in January 2019 for eligible articles that fulfilled all 3 of our chosen inclusion criteria: (A) case/cases with pathology in the tissue of the eyeball itself, the ocular adnexa, the extraocular muscles, and the optic nerve

Fig. 1. Flow diagram of the study selection process.

were excluded; (B) detection of *Borrelia* spp. within the affected eye tissue; and (C) only studies written in English, Swedish, Danish, or Norwegian were included.

Search Strategy

In the scientific literature search, we included references comprising research on adults, young people, and children according to the predefined selection criteria. To construct the search string, the PubMed was first extensively searched in a nonsystematic manner to find articles fulfilling the inclusion criteria, either directly or through relevant references. This initial search yielded 12 articles that met the inclusion criteria. Subsequently, with the support of a medical librarian, a search string was constructed in a way that was assumed to capture all relevant studies and that also captured the 12 studies from the nonsystematic search: *(lyme OR borrelia) AND (eye OR opht* OR blind* OR ocul*) AND (biopsy OR immunohisto* OR histology OR PCR OR polymerase OR tissue OR cytolog* OR microbiolog* OR microscop*) AND (humans)*. Two authors (B. Lindström and B. H. Skogman) independently systematically searched the PubMed for studies in January 2019 using the PubMed search string based on the eligibility criteria. Reference

lists of articles that were considered relevant were searched. On the gathered studies fulfilling our inclusion criteria, a citation reference search was made through Google Scholar.

Data Extraction and Quality Assessment

The authors mentioned above independently reviewed the studies using a protocol (online suppl. material 1) to assess the clinical plausibility of *Borrelia* causing the eye condition. In case of disagreement, a third author (L. Tallstedt) made a final judgment. The quality of laboratory diagnosis in the reported cases was assessed with a protocol (online suppl. material 2) by the author K. Nilsson. As a secondary aim, the studies found with evidence for ocular *Borrelia* infection were evaluated for the possibility of good evidence-based treatment for ocular *Borrelia* infection. Disagreements between the reviewers were discussed and resolved through consensus.

Results

Search Results

Our search strategy by PubMed on January 8, 2019, captured 257 studies with the search string (Fig. 1). Of these, 12 studies, found through direct hits, were assessed eligible and included for full-article review and quality assessment (Duray and Steere [4]; Kauffmann and Wormser [5]; Karma et al. [6]; Preac-Mursic et al. [7]; Clinch et al. [8]; Schubert et al. [9]; Karma et al. [10]; Hilton et al. [11]; Linna et al. [12]; Mikkila et al. [13]; Mikkila et al. [14]; and Dietrich et al. [2]). No additional studies were found through the reference lists. Citation references yielded one additional study, Hassan M. [15], that was included. Two out of the 13 primary studies included from the search were later excluded, Karma et al. [10] and Mikkila et al. [13] since they contained duplicate cases from other articles by Karma et al. [6] and Mikkila et al. [14], see The Finnish cases below. Eleven studies were included as shown in Figure 1, of which all passed the clinical evaluation protocol. A new PubMed search with the same search string was conducted on first of April 2021, which yielded 31 new articles, none of which met the established inclusion criteria.

Laboratory Diagnostic Categories

It is claimed that in these cases *Borrelia* has been identified in the cornea, conjunctiva, the aqueous fluid, and the vitreous. The laboratory diagnostic characteristics of the included studies are presented in Table 1 and have been ranked into three categories: groups A, B, and C, based on their diagnostic quality. Group A represents substantial evidence of *Borrelia* detection, when the laboratory method corresponds to the genus level (*Borrelia* spp. or *Borrelia burgdorferi sensu lato*) or species level (e.g., *B. afzelii*, *B. burgdorferi sensu stricto*), together with a sufficiently detailed laboratory description to assume a correct performance. The studies marked in group B only have partial evidence for a strategy that admits the detection of *Borrelia*, but it is still plausible to assume that *Borrelia* was detected. They have a sufficient description of the laboratory technique, and the assumption of *Borrelia* infection is strengthened by either serology or EM, but the method used for direct detection of *Borrelia* cannot reach the level of genus or species. Those studies that did not fulfill the criteria, which correspond to group A or B, are marked as group C and are considered to have weak evidence for the detection of *Borrelia* infection.

PCR as a Diagnostic Tool

PCR has different diagnostic levels that correspond to the genus or species depending on the primers used. Dietrich et al. [2] claim they have identified the species *Borrelia garinii* with PCR. They used the *flaB* and *ospA* genes that might enable detection to species level. However, a fundamental requirement should be to present the primer target and the size of the amplified fragment, and this information is missing. Therefore, their diagnostic level is set at the genus level. None of the included cases reached the level of species.

Microscopy as a Diagnostic Tool

Four studies using microscopy had a sufficient description of their laboratory work; Duray and Steere [4]; Kauffmann and Wormser [5]; Linna et al. [12]; and Dietrich et al. [2]. Microscopy by itself cannot adequately sort out *Borrelia* from other potential spirochetes. We assume that microscopy without the help of other diagnostic methods can reach the family level, which *Borrelia* shares with the human pathogen *Treponema*. *Treponema pallidum* (syphilis) can cause similar manifestations to *Borrelia* as described by Karma and Mikkila [16]. In serology, the risk of cross-reactivity between *Treponema* and *Borrelia* is substantial; therefore, a positive *Borrelia* serology is always checked for *Treponema*, and hence, all cases with positive serologies can be counted on to have been tested negative for *Treponema* as shown in Table 1. A negative *Borrelia* serology is not tested for *Treponema*, but it is not likely to contain *Treponema* antibodies due to the cross-reactivity with *Borrelia*. Linna et al. [12] used tandem scanning confocal microscopy and Dietrich et al. [2] electron microscopy, both established methods which enable detailed examination. Duray and Steere [4] and Kauffmann and Wormser [5] used the common silver nitrate Dieterle staining method for light microscopy of spirochetes. Dietrich et al. [2] could achieve the genus level *Borrelia* through the additional use of PCR. Duray and Steere, Kauffman and Wormser, and Linna et al. [4, 5, 12] had no supplementary method to microscopy, and they assessed to reach the level of the family *Spirochaetaceae*. Schubert et al. [9] used Papanicolaou staining which is not a fully established staining of spirochetes, and repeated serology for *Borrelia* was negative. Moreover, Shubert et al. [9] did not use defined *Borrelia* species as a control to verify the usefulness of their Papanicolaou staining, which is a mandatory requirement as they used a stain that is more appropriate for cytopathological assessment. They can therefore be assumed not to have used a correct laboratory method; they are assessed to reach the level of family *Spirochaetaceae*.

Table 1. Laboratory aspects of cases of *Borrelia* eye infection

Study	Eye tissue	Laboratory method	Accuracy, given correct laboratory work	Satisfying laboratory description	EM/TB	Anti- <i>Borrelia</i> antibodies	Syphilis assays
A	Dietrich et al. [2]	ELM/PCR	Genus – <i>Borrelia</i>	Species, no. Genus, yes	No	S test – S-IgG+	N/A
	Hilton et al. [11]	PCR	Genus – <i>B. burgdorferi</i>	Yes	N/A	S-IgG+	Negative
	Karma et al. [6]	PCR	Genus – <i>Borrelia</i>	Yes	No	S–, CSF–, retest in another lab S-IgG/IgM+	Negative
	Mikkilä et al. [14]	PCR	Genus – <i>Borrelia</i>	Yes	TB EM	S-IgG+, CSF–	Negative
B	Duray and Steere [4]	Microscopy	Family – Spirochaetaceae	Yes	EM	N/A	N/A
	Kauffmann et al. [5]	Microscopy	Family – Spirochaetaceae	Yes	EM	S test –	Negative
	Linna et al. [12]	TCSM	Family – Spirochaetaceae	Yes	TB	S-IgG+	Negative
	Preac-Mursic et al. [7]	Culture WB	Genus – <i>B. burgdorferi</i>	Borderline	TB	S-IgG+	Negative
C	Clinch et al. [7]	Culture	Family – Spirochaetaceae	No	N/A	N/A	N/A
	Hassan et al. [15]	PCR	Genus – <i>Borrelia</i>	No	No	N/A	Negative
	Schubert et al. [9]	Microscopy	Family – Spirochaetaceae	No	No	S test	Negative

Group A, substantial evidence for the detection of *Borrelia*; group B, partial evidence for the detection of *Borrelia*; and group C, weak evidence for the detection of *Borrelia* infection. ELM, electron microscopy; N/A, not available; –, negative; +, positive; S, serum.

Culture as a Diagnostic Tool

Two studies used culture, Preac-Mursic et al. [7] and Clinch et al. [8]. This is the only methodology that can prove a finding of viable *Borrelia*. Clinch et al. [8] have not reported how they determined their cultured organism to be *Borrelia*. We assume that they have used microscopy, which does not provide precision in species determination. Therefore, the diagnostic level is set at the family level, yet it is difficult to assess as the laboratory performance is insufficiently described. The case was assessed as having weak evidence for laboratory detection of *Borrelia*. Preac-Mursic et al. [7] have used monoclonal antibodies and Western blot (WB) techniques to demonstrate their cultured *Borrelia*. The diagnostic precision is estimated to be at the genus level. Preac-Mursic's description of the method of culture and WB are acceptable, but the presentation of the WB results is sparse, which was why the quality of the laboratory performance was evaluated as “borderline,” and the laboratory evidence was assessed as partial.

Clinical Diagnostic Aspects

The clinical diagnostic aspects of the cases are summarized in Table 2. Hassan et al. [15] did not present clinical information about the case but did to some extent present the workup for differential diagnosis. Clinch et al. [8] and Hilton et al. [11] did not present any clinical information or information about differential diagnostics. Although it was difficult to determine the clinical probability of *Borrelia* infection in these three studies, we decided to include them for further evaluation. As presented in Table 2, in some of the cases, EM or a TB has not been reported. Some cases showed no, or few, extraocular signs or symptoms.

Treatments Used

The different types of treatment are summarized in Table 2. In the case reported by Kauffmann and Wormser [5], orbital cellulitis was suspected and nafcillin, gentamicin, and neomycin-polymyxin were administered as treatment. Although this treatment was probably not primarily aimed at a suspected *Borrelia* infection, we have chosen to present it in the table (Table 2). Three of the cases gave no information about treatment, and it concerns Duray and Steere [4], Clinch et al. [8], and Hassan [15]. Two of the cases, Mikkilä et al. [14] and Dietrich et al. [2], seemed to have successfully treated all signs of ocular infection. They had both in common that intravenous ceftriaxone was used and that the infection was of the ocular surface, i.e., keratopathy and conjunctivitis.

Table 2. Clinical aspects of cases of *Borrelia* eye infection

	Study	Eye condition	Other possibly related manifestations	Reported TB	Antibiotics	Immunosuppressive therapy
A	Dietrich et al. [2]	Crystalline keratopathy	Arthritis	No	Ceftriaxone iv 2 wk and topical tetracycline 2 yr	Systemic mtx, cs, and cs drops
	Hilton et al. [11]	Pars planitis	N/A	N/A	Ceftriaxone iv 10 d and po macrolide 2 mo	N/A
	Karma et al. [6]	Neuroretinitis	Fever, dizziness, and peripheral neuropathy	No	Ceftriaxone iv 3 wk and cefuroxime po 1 mo	No
	Mikkilä et al. [14]	Conjunctivitis	EM, fatigue, migratory arthralgia, vertigo, tinnitus, and facial pain	Yes	Repeated ceftriaxone iv 2 wk and po amoxicillin + probenecid po 100 d	No
B	Duray and Steere [4]	Uveitis	EM	No	N/A	N/A
	Kauffmann et al. [5]	Panuveitis	EM, headache, fever, chills, nausea, and vomiting	No	Cefazolin, nafcillin, and gentamycin iv; chloramphenicol and gentamycin ivt; topical neomycin-polymyxin B; and sulphafurazole	cs iv and cs drops
	Linna et al. [12]	Stromal keratitis and endotheliitis	Lower extremity pain and weakness	Yes	Doxycycline po 3 mo	N/A
	Preac-Mursic et al. [7]	Panuveitis	No	Yes	Doxycycline po 4 wk, twice	Yes. Not specified
C	Clinch et al. [7]	Keratitis	N/A	N/A	N/A	N/A
	Hassan et al. [15]	Iritis	N/A	N/A	N/A	N/A
	Schubert et al. [9]	Panuveitis	No	No	Ceftriaxone iv 3 wk and doxycycline iv 3 wk	Cs iv (+acyclovir iv)

Group A, substantial evidence for the detection of *Borrelia*; group B, partial evidence for the detection of *Borrelia*; and group C, weak evidence for the detection of *Borrelia* infection. cs, corticosteroid; d, days; iv, intravenous; IVT, intravitreal treatment; mo, months; mtx, methotrexate; N/A, not available; po, peroral; wk, weeks; yr, years.

However, in both cases, other antibiotics had also been given, and the description of the final clinical result and the follow-up time could have been more precise. The other five cases had all unclear results of treatment. Treatment was often followed by improvement. None of the cases had complete resolution of possible infectious signs.

The Finnish Cases

Four studies, Karma et al. [6], Karma et al. [10], Mikkilä et al. [13], and Mikkilä et al. [14], published in the 1990s by a group of Finnish authors, met the inclusion criteria. Because of case duplicates, only two unique includible cases were found. One of the articles, from January 1999, described the laboratory work done in both cases [13]. One is a case of a 15-year-old girl with vitritis and retinitis pigmentosa-like retinal changes with positive PCR in the vitreous and CSF. This was first published in 1993 [6]. Later, that patient was also described as having neuroretinitis in an article published

in 1995 [9], as well as in two later articles [13, 14]. To evaluate this case, we have used the original report [5] and added information about the laboratory work published in the article from January 1999 [13]. The other case is a woman with follicular conjunctivitis with positive PCR from the conjunctiva. That case was originally published in the study from January 1999 [13], describing the laboratory diagnosis. The complementary clinical description of the case was later published in July 2000 by Mikkilä et al. [14].

Studies in Other Languages

Two articles in German were found but not analyzed in detail due to linguistic interpretation difficulties. These are Meier et al. [17] and Lohmann et al. [18]. Meier et al. [17] claimed that with microscopy that they had found *B. burgdorferi* in the vitreous of an eye with endophthalmitis. Lohmann et al. [18] claimed PCR detection of *B. burgdorferi* in the corneas of two eyes with keratitis.

Discussion

Final Outcome of Eligible Cases

This study was conducted to assess the evidence and state of the art that can be assumed to support an ocular infection of *Borrelia* spp. Apart from our case, we found 11 additional cases where authors claimed *Borrelia* to have been directly detected in relevant pathological eye tissue: Duray and Steere [4], Kauffmann and Wormser [5], Karma et al. [6], Preac-Mursic et al. [7], Clinch et al. [8], Schubert et al. [9], Hilton et al. [11], Linna et al. [12], Mikkila et al. [14], Dietrich et al. [2], and Hassan et al. [15]. In four of these 11 cases, we assessed them to have substantial laboratory evidence of *Borrelia* infection, and these are Karma et al. [6], Hilton et al. [11], Mikkila et al. [14], and Dietrich et al. [2]. In four additional cases, we assessed it was reasonable to suspect *Borrelia* infection: Duray and Steere [4], Kauffmann and Wormser [5], Preac-Mursic et al. [7], and Linna et al. [12] and for a further three: Clinch et al. [8], Schubert et al. [9], and Hassan [15]. Sufficient evidence to conclude a *Borrelia* infection as a cause was lacking. Two additional articles in German were found that were not included due to the language barrier. Consequently, these reports add more evidence to the concept of ocular *Borrelia* infection than stated by the French guidelines on Lyme Disease of 2019 by Gocko et al. [1].

Assessment of the Usefulness of Laboratory Methods

Microscopy without using PCR or direct immune detection of *B. spirochetes* has its limitations. Two other genera of spirochetes known as human pathogens are *Leptospira* and *Treponema*. *Leptospira* can usually be distinguished under the microscope through its specific morphology. *Treponema* species, causing the diseases syphilis, bejel, yaws, and pinta, shares the same family as *Borrelia* and is less easy to distinguish under the microscope. Many of the ophthalmological manifestations seen in Lyme disease have also been observed in syphilis [16]. It is therefore crucial to exclude laboratory evidence of syphilis when *Borrelia* is suspected using only microscopy. In theory, other spirochetes, perhaps not yet known as human pathogens, could be mistaken for *Borrelia* under the microscope. Also, if a correct staining for spirochetes is not performed, tissue debris can be mistaken for spirochetes [19]. The possibility of indirectly finding evidence for uveitis caused by *Borrelia* through CSF analysis of anti-*Borrelia* antibodies or PCR has been discussed [20, 21]. In the case of simultaneous neurological symptoms, optic neuritis, or possibly neuroretinitis, such an approach might be

feasible. If that is not the case, we believe that aspirations or biopsies of relevant ocular content are more accurate and offer better differential diagnostic opportunities.

Seronegative *Borrelia* infection is a known entity, most often associated with EM [22]. In the group A of cases with substantial evidence for detected *Borrelia*, the patient presented by Dietrich et al. [2] was found seronegative. In the Karma et al. [10] report, the patient was seronegative in the first test several months after contracting her eye disease, but a retest of the same sample in another laboratory showed positive s-IgM/IgG [10]. In the group C category with weak evidence for detected *Borrelia*, the patient described by Schubert et al. [9] was seronegative. Some of the cases had neither known TBs nor EM. This highlights that looking for *Borrelia* in ocular tissue samples can be relevant even if there is a lack of positive serology or other classical clues for borreliosis.

In this article, we have only discussed *Borrelia* infection of the eye. Also, an indirect affection to the eye by *Borrelia* is possible. Murillo et al. [23] described a case of probable immune-based keratopathy secondary to a likely *Borrelia* infection of the eyelid.

Evaluation of Treatment Strategies

Evaluation of treatment in the cases included in this review was not the primary aim. However, only two of the studies seemed to have noticed clear effects of treatment [2, 14], and in the rest of the studies included, treatment showed more ambiguous results. This does not mean the treatment in the other cases were without effect but that the case descriptions were too insufficient to draw clear conclusions. The common tendency for relapses after treatment of ocular borreliosis is described in the earlier literature [24]. Based on what emerges from this review of published cases of well-proven ocular *Borrelia* infection, larger studies are needed to determine which treatment for ocular *Borrelia* infection is optimal.

Lyme disease can sometimes be difficult to cure as persistent symptoms can be observed even after rigorous treatment and is called by some researchers as posttreatment Lyme disease syndrome. It is hypothesized that it could be due to the infection not being eradicated or a hyperresponsive immune reaction to antigenic debris of dead *B. spirochetes* [25–27].

There is, as yet, no established antibiotic treatment for intraocular *Borrelia* infection [28, 29]. To our knowledge, either oral doxycycline [28, 30] or daily intravenous antibiotics such as cephalosporins or penicillins for two to three weeks are currently the two main types of antibiotic treatments for ocular borreliosis.

Doxycycline is effective in neuroborreliosis; however, it can be questionable in intraocular disease. To our knowledge, there are few studies of its intraocular penetration. With no references, the French guidelines for Lyme disease state that doxycycline should not be given in intraocular disease due to poor intraocular penetration [1]. Two studies of systemic doxycycline in horses [31, 32] and one study of systemic doxycycline in rabbits [33] showed poor intraocular concentrations of doxycycline. In our material, we had three cases that used oral doxycycline (Linna et al. [12], Preac-Mursic et al. [7], and our case). In none of the cases was the intraocular inflammation eradicated. Preac-Mursic et al. cultured viable *Borrelia* from the iris following two 4-week courses with oral doxycycline [7]. Thus, from what we have found in these case reports, the usefulness of doxycycline in intraocular *Borrelia* infections needs to be further studied. Intravenous treatment for 2 to 3 weeks has practical and economical inconveniences, also when considering the uncertain outcomes. Two of the cases in this review had to stop long-term intravenous cephalosporin treatment due to negative effects on hematopoiesis [9, 11]. Biliary complications [34] and pseudomembranous colitis [35] from long-term treatment with ceftriaxone for Lyme disease are also described. In a review regarding the intraocular penetration of systemic antibiotics, meropenem achieved the best-documented therapeutics levels, and the cephalosporins ceftriaxone, cefazolin, and ceftazidime presented the 'second-best' evidence for intraocular penetration as opposed to cipro- and levofloxacin, aminopenicillin, piperacillin, and clarithromycin where available data did not support use in these situations [36]. Oral antibiotics would be a more convenient route of systemic antibiotics. Moxifloxacin and linezolid are both antibiotics with the best available evidence for intraocular penetration, better than cephalosporins [36]. Both also have good laboratory evidence for being effective against *Borrelia* [27]. In theory, oral treatment by moxifloxacin or linezolid is an interesting alternative for treating intraocular *Borrelia*. Also, trimethoprim shows some laboratory evidence indicating that it can be effective [36, 37]. Interestingly, disulfiram, the substance commonly known for the treatment of alcoholism, is under study as a potential future drug for long-term treatment of relapsing borreliosis [38].

Intravitreal antibiotic treatment is an interesting but seldom discussed alternative. Ampicillin, cefazolin, ceftazidime, clindamycin, erythromycin, moxifloxacin, oxacillin, and vancomycin are antibiotics that can be used for intravitreal treatment [39], and all of these have proved to be effective against *Borrelia* in vitro, of which cefazolin

had the most favorable values of minimal inhibitory concentration and minimal bactericidal concentration [27]. When intravitreal antibiotics are used, one might consider giving simultaneous intravenous doses of the same antibiotic to maintain the antibiotic intraocular concentration for a longer period [39].

Jarish Herxheimer's reaction (JHR) is a bothersome inflammatory complication when killing spirochetes, which usually occurs within 24 h. Administration of corticosteroids prior to antimicrobial treatment has been used to prevent development of severe JHR [40]. With the guidance of these studies, a model for treating ocular borreliosis might be intravitreal cefazolin, possibly with 1-2 doses of intravenous cefazolin the same day and simultaneously starting an oral course of moxifloxacin or linezolid. In the case of any intraocular JHR, it would be optimal to undertake a clinical control within 24 h and possibly to add a preventive dose of topical or systemic corticosteroids.

Limitations of This Study

In this review, we have focused on the *B. spirochetes* causing Lyme disease and not on other *Borrelia* species causing louse-borne relapsing fever and tick-borne relapsing fever, which are both diseases known to have ophthalmological manifestations [41, 42]. We have also not searched for possible eye manifestations caused by louse-borne relapsing fever or tick-borne relapsing fever. Another limitation in our review is that we have only used the databases of PubMed and Google Scholar. We have focused on cases with evidence of laboratory detection of *Borrelia* in ocular tissues. Due to the low number of cases with this kind of evidence, it is pragmatic to also look at cases with indirect laboratory evidence but high clinical suspicion, as done by others [24]. There are cases described with high clinical and indirect laboratory suspicion of ocular *Borrelia* infection where ocular tissue samples have not detected *Borrelia*. A balanced clinical assessment must be given priority over individual test results [24]. Finally, it should also be remembered that evidence of *Borrelia* species in ocular tissue does not necessarily mean that *Borrelia* is the cause of the current ocular pathology.

Conclusion

This systematic review which focuses on the diagnosis of *Borrelia* infection in the eye, including all reported cases and our case report, supports evidence of ocular infection of *Borrelia* species. However, the amount of data are

quite small, why the conclusions rely on detailed assessments of the individual reports. We can conclude that seronegative *Borrelia* infection occurs, why in these cases, looking for *Borrelia* in ocular tissue samples can be relevant. Further that microscopy without using PCR is not sufficient to confirm the diagnosis of *Borrelia* infection in ocular tissue. In the articles studied, there is also currently no clear evidence of a golden standard treatment for ocular *Borrelia* infection. However, the selection of articles was not focused on treatment why no definitive conclusion can be drawn, but from what emerged, oral doxycycline and amoxicillin were not always optimal drugs for the treatment of intraocular *Borrelia* infection. Further studies on treatment strategies are therefore warranted.

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Statement of Ethics

Written informed consent was obtained from the patient in the case report to publish details of the patient's medical case. For the rest of the study, an ethics statement is not applicable because this study is based exclusively on the published literature.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Björn E. Lindström contributed to study design, manuscript writing – original draft, and evaluation of cases. Barbro H. Skogman contributed to study design, manuscript writing – review and editing, and evaluation of cases. Annika K. Lindström contributed to study design and manuscript writing – review and editing. Leif Tallstedt and Kenneth Nilsson contributed to study design, manuscript writing – review and editing, and evaluation of cases. All the authors approved the submitted version of the manuscript.

Data Availability Statement

The evaluation sheets of the review are added as online supplementary material.

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