

Diagnosis of Lyme-associated uveitis: value of serological testing in a tertiary centre

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ABSTRACT

Aims To determine the frequency and clinical presentation of Lyme disease in patients with uveitis and to assess the value of *Borrelia burgdorferi* serological testing.

Methods Retrospective study on all patients with uveitis who were referred to our tertiary hospital were serologically tested for Lyme in our laboratory between 2003 and 2016. Screening consisted of determining *B. burgdorferi* serum IgG and IgM by ELISA method. The patient's serology was considered as positive if the ELISA-positive result in IgM and/or IgG was confirmed by an immunoblot positive in IgM and/or IgG. Lyme-associated uveitis was diagnosed based on serological results as well as response to antibiotics and exclusion of other diagnosis.

Results Of the 430 patients with uveitis (60% women, mean age 49 years) fulfilling inclusion criteria, 63 (14.7%) had an ELISA-positive serology, confirmed by immunoblot for 34 patients (7.9%). The diagnosis of Lyme-associated uveitis was finally retained in seven patients (1.6%). These patients reported either a previous exposure including tick bite or forest walks (n=5), symptoms suggestive of Lyme disease (n=5) and resistance to local and/or systemic steroids (n=7). Among the remaining 27 positive patients, 22 had other established aetiologies and 5 other were unclassified.

Conclusion The seroprevalence of *B. burgdorferi* among our patients with uveitis was 7.9% compared with 6%–8.5% in the general French population which leads to a low predictive value of serological testing. Its use should be reserved for patients with unexplained uveitis, an exposure history, systemic findings suggestive of Lyme disease and steroids resistance.

INTRODUCTION

Lyme is a multisystemic infectious disease caused by spirochetes of the *Borrelia burgdorferi* sensu lato genogroup, found in Europe, North America and northern Asia.¹ The regional disparities are due to differences in prevalence of the arthropod vector and reservoir animals.² The spirochete is transmitted essentially from May to September by certain species of Ixodes ticks which requires attachment to the host for 17 to 72 hours,³ depending on the species of Lyme *Borrelia* and ticks. In France, incidence is around 43/100 000,^{4,5} which is average for Europe, and it considered stable in the last couple years. Most cases are found in children from 5 to 9 and adults between 50 and 64 years old.⁴ The seroprevalence in general population is 6% to 8.5%, and can reach 14% to 22% in field workers,

of whom 83% remember tick bites.⁴ In the Rhone-Alpes region where our study was done, incidence is even higher (111/100 000), which might lead to an even higher seroprevalence. However, no regional data has been collected.

The Centers for Disease Control and Prevention (CDC, USA) recommends serological screening only in symptomatic patients with a risk of exposure to black-legged ticks.⁶ However, as there is a lot of misinformation about Lyme disease, patients as well as physicians are becoming increasingly worried about it leading to 3.4 million serological tests annually in the USA with a cost of \$492 million.⁷ This mass screening is unnecessary because the diagnosis of Lyme disease is based not only on laboratory testing but on a set of arguments: possible exposure (endemic area, summer season, tick bite), compatible symptoms and positive serology using the two-tiered method.^{3,8} This method consists of an ELISA serology confirmed by immunoblot if positive or inconclusive.

The symptoms of Lyme disease are very varied and can cause skin lesions (classically early erythema migrans in 65% to 89% of cases,^{3,4,9} and later *Borrelia* lymphocytoma or acrodermatitis chronica atrophicans), arthritis, neurological manifestations (meningoradiculoneuritis, meningitis and peripheral facial palsy) and cardiac involvement (atrioventricular block or myopericarditis). Ophthalmological symptoms are rather rare as they appear in less than 1% of Lyme cases.⁹ It can cause all type of uveitis, although it remains a rare cause, also estimated at less than 1% of all uveitis.¹⁰

There are no clear international recommendations concerning paraclinical exams necessary in the initial investigation of a uveitis. A recent French study (Ulisse) recommended only a blood count, sedimentation rate, C-reactive protein, syphilis serology, thoracic X-ray and a tuberculin skin test (5-TU).¹¹ However *Borrelia* serology is still widely prescribed in first intention when exploring a uveitis.¹² The aim of our retrospective study was: (1) to determine the frequency and clinical presentation of Lyme disease in a population of patients referred to our tertiary centre for the diagnosis of uveitis; (2) to assess the value of serological testing.

PATIENTS AND METHODS

We performed a monocentric retrospective study on 1006 uveitis patients who were referred to the internal medicine department of Croix Rousse Teaching Hospital, a tertiary centre in Lyon, France, between 1 May 1 2003 and 31 July 31 2016.



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Among them, we included the patients for whom a serological *B. burgdorferi* testing was performed in the referring bacteriological laboratory of our university hospital, excluding serologies performed in private labs. There were no specific criteria for when to perform *Borrelia* serology. The serology results were extracted from our laboratory computers' database. According to French law (no. 2004–806, 9 August 2004) and because the data were collected retrospectively and patient management was not modified, this study did not require research ethics committee approval. It was conducted in accordance with the law on data protection (no. 2004–801, 6 August 2004).

Testing consisted of determining *B. burgdorferi* serum IgG and IgM by ELISA method, done and interpreted in our lab using different multipipettors and ELISA plate readers as technology evolved: BEP2000 followed by BeeFree and BepIII, according to the kit supplier's recommendation. Two reagents were used during the time of the study over three times periods as we missed the call for tenders. From May 2003 to January 2010 and then from March 2013 to July 2016, we used Siemens Enzygnost Lyme link VlsE/IgG and Enzygnost Borreliosis/IgM (Marburg, Germany). From January 2010 to March 2013 we used antibodies anti-*Borrelia* Plus VlsE (IgG) with antibodies anti-*Borrelia* (IgM) EUROIMMUN AG Seekamp 31 D-23560 (Lübeck, Germany). Positive and borderline ELISA results were subsequently confirmed by an immunoblot to exclude false positives, according to the two-tiered serology standard recommended by the CDC. The bacterium proteins and reagent were EUROLINE-WB Anti-*Borrelia* (IgG), EUROLINE-WB Anti-*Borrelia* (IgM), Euroimmun France, selected following the manufacturer's instructions and the National Reference Center for Lyme Disease in Strasbourg's recommendations. We applied the European's recommendation to determine the positivity of the results: at least two positive bands for IgG and one for IgM. In case of indeterminate immunoblot results, a second serum sample was analysed similarly 4–6 weeks later.

The patient's serology was considered as positive if the ELISA's positive result in IgM and/or IgG was confirmed by an immunoblot positive in IgM or IgG. A negative Immunoblot or indeterminate immunoblot on repeat was considered as negative. All patients were also screened for *Treponema pallidum* to exclude cross-reactivity. Some seropositive patients underwent a PCR Lyme search in cerebrospinal and aqueous or vitreous fluids depending on clinical presentation. We used RealCycler BBUR, Progenie Molecular, Edificio Progenie, Spain. RealCycler BBUR

is an in vitro diagnostic kit of reagents which allows real-time PCR detection of *B. burgdorferi* DNA in clinical samples, using SmartCycler (Cepheid).

For all patients, demographics, anatomical classification of uveitis, medical history (tick exposure, clinical symptoms), final diagnosis and treatment were derived from their medical records.

The diagnosis of Lyme associated uveitis was made using three criteria: (1) a positive ELISA serology confirmed by immunoblot; (2) an exclusion of other uveitis entities (negative chest CT scan, negative interferon-gamma release assays for *Mycobacterium tuberculosis* infection (Quantiferon); (3) a therapeutic test with a positive response to the antibiotic treatment. Clinical plausibility was also considered based on possible exposure (endemic area, summer season, tick bite, walks in forest), extra ophthalmological clinical symptoms and uveitis resistance to steroids alone (local and/or systemic).

RESULTS

A total of 430 uveitis patients (60% women, mean age 49 (6–92)) were included in our study. The demographics and uveitis characteristics of the population are summarised in table 1. All anatomical types of uveitis were found: anterior (n=106; 24.7%), intermediate (n=50; 11.6%), anterior+intermediate (n=33; 7.7%), posterior (n=92; 21.4%), intermediate+posterior (n=31; 7.2%) and panuveitis (n=118; 27.4%). Most presented bilateral uveitis (n=265; 61.6%).

Of the 430 patients screened for Lyme (ELISA), 63 (14.7%) had a positive serology: 41 tested positive in IgG and 27 in IgM, including 5 patients positive for both IgG and IgM. All of them had an immunoblot, which confirmed the positivity for 34 patients (7.9%): 29 in IgG and 16 in IgM, including 11 positive for both IgG and IgM. Three hundred and thirty-five (78%) patients were tested by ELISA Siemens Enzygnost + Euroimmun Immunoblot with 23 positive results, while 95 patients were tested by ELISA Euroimmun + Immunoblot Euroimmun with 11 positive results (p=0.13).

The diagnosis of Lyme associated uveitis was finally retained in seven patients (20.6% of these positive patients, that is, 1.6% of the screened cohort), after an antibiotic course with intravenous ceftriaxone 1 or 2 g/day for 3–4 weeks (n=6) or oral doxycycline for 4 weeks (n=1). The treatment was rapidly effective in all patients.

Table 1 Demographics of uveitis patients screened for *Borrelia burgdorferi*

	All patients (n=430)	Seropositive patients (n=34: 7.9%)	Lyme uveitis (n=7: 1.6%)
Age (mean, (extremes))	49 (6–92)	55 (20–79)	55 (38–70)
Sex, n (%)			
Male	174 (40.5)	21 (61.8)	5 (71.4)
Female	256 (59.5)	13 (38.2)	2 (28.6)
Anatomic classification, n (%)			
Anterior uveitis	106 (24.7)	8 (23.5)	1 (14.3)
Anterior + intermediate	33 (7.7)	5 (14.7)	2 (28.6)
Intermediate	50 (11.6)	4 (11.7)	1 (14.3)
Intermediate + posterior	31 (7.2)	4 (11.7)	1 (14.3)
Posterior	92 (21.4)	7 (20.6)	2 (28.6)
Panuveitis	118 (27.4)	6 (17.6)	0 (0)
Side			
Unilateral	164 (38.1)	14 (41.2)	6 (85.7)
Bilateral	266 (61.9)	18 (52.9)	1 (14.3)

Table 2 Other aetiologies of uveitis in *Borrelia burgdorferi* seropositive patients

Aetiology	N	%
Sarcoidosis	11	40.7
Unknown	5	18.5
Herpes simplex virus	3	11.1
Lymphoma	2	7.4
Crohn's disease	1	3.7
Toxoplasmosis	1	3.7
Leptospirosis	1	3.7
Posner-Schlossman	1	3.7
Multiple sclerosis	1	3.7
Tuberculosis	1	3.7
Total	27	100

Within the Lyme-associated uveitis (n=7, 71.4% male, mean age 55.3 (38–70), 85.7% unilateral), seven were resistant to cortisone alone, administered locally (topic and subconjunctival injections) for four patients and locally+orally for three. All uveitis were active, and no distinction of intensity could be made based on aetiology. Almost everyone practised forest walks (n=6), of whom two remembered tick bites. The extraophthalmological manifestations included: erythema migrans (n=1), arthritis (n=3) and borrelial lymphocytoma (n=1). None of the cerebrospinal (n=7) and ocular (aqueous or vitreous) (n=4) fluids PCR analysis were positive, but two patients had lymphocytic meningitis.

Among the remaining 27 positive patients, 22 had other established aetiologies of which sarcoidosis was the most frequent (see table 2). For the five uveitis considered as unclassified, the diagnosis of Lyme was not retained because of the efficacy of the steroid treatment alone for three patients, and because of the inefficacy of ceftriaxone treatment for one patient. The last patient was not treated because the multifocal choroiditis lesions were inactive at the time of diagnosis, so the imputability of Lyme disease was considered as uncertain. There was no extraophthalmological symptom for these patients. We could find no correlation between these aetiologies and seropositivity as the repartition was consistent with that of the whole cohort. Indeed, the main aetiologies found for the 430 patients were unclassified (n=112), sarcoidosis (n=79), human leukocyte antigen B27 (n=24), tuberculosis (n=18), multifocal choroiditis (n=14), Fuchs' uveitis and Posner-Schlossman syndrome (n=11), lymphoma (n=10) and herpes simplex virus (n=10). Many more causes were found in smaller numbers.

DISCUSSION

The seroprevalence of Lyme borreliosis in our series is 7.9% for all tested patients with uveitis, which is close to the seroprevalence in France's general population (6% to 8.5%).⁴ A diagnosis of Lyme disease was made in 20.6% of these positive patients (1.6% of the screened cohort). The ophthalmological presentation was varied and non-specific. In all cases, there were guiding elements: possible exposition, extraocular signs and resistance to steroids (local +/- systemic).

Routine serological screening for *B. burgdorferi* in patients with uveitis, in the lack of clinical orientation, should be prohibited for multiple reasons.

First, a positive serology does not mean the patient has an active infection.^{3 13 14} IgM and IgG may persist for years without reactivation of borreliosis.⁹ Accordingly, seropositivity can be

coincidental, corresponding to the spread in general population. Second, uveitis is a rare manifestation of Lyme disease and, conversely, Lyme is a rare cause of uveitis.^{2 3 10 15} The two-tiered testing has a very high sensitivity (97%–100% after the acute phase, negative predictive value close to 100%) and a very high specificity (above 99%).¹⁶ There are rare causes of false negative: (1) very early screening in the first 2 weeks after the tick bite when the IgM have not appeared yet; (2) early antibiotic treatment and (3) immune complex formations which make immunoglobulins undetectable.¹⁴ The false positive are mainly due to cross-reactivity with bacterium endowed with similar antigens (*Treponema*, rickettsia and leptospira).¹⁷ Although the two-tiered method is a very reliable test, the low prevalence of Lyme disease in patients with uveitis makes serological screening not sufficient to confirm Borreliosis.^{13 14 16} As described by Tugwell *et al*¹⁸ when the pretest probability of Lyme disease is low (under 0.2, which is the case for patients with non-specific symptoms even in endemic areas), testing will result in more false positive than true positive. If pretest probability is high (over 0.8, which is the case of patients presenting erythema migrans after a tick bite), serology is not necessary for diagnosis.

Based on these limitations, Lyme serology should be carefully prescribed. We suggest in addition to the CDC criteria⁶ for diagnosis of Lyme uveitis, described above, that we consider the exclusion of other uveitis entities and the response to antibiotics. These criteria are similar to those proposed for the diagnosis of neuro Lyme (in addition to laboratory tests) in a study conducted on 123 patients with neurological symptoms and positive cerebrospinal fluid anti-*Borrelia* antibodies.¹⁹ They can also be compared with the diagnosis of possible intraocular tuberculosis, which may occur in geographic areas where tuberculosis is low in incidence and identification of *Mycobacterium tuberculosis* either in ocular fluids or pulmonary specimens is exceptional.²⁰

In a recent retrospective Dutch study conducted on 1126 patients with uveitis, Kazi *et al* recently confirmed the systematic screening of patients with uveitis had no value.¹² In their tertiary centre, seroprevalence was 3.7%, which is slightly lower than the prevalence in their general population. Of the 14 *Borrelia*-seropositive patients with unclassified uveitis, five patients were treated with antibiotics, without mention of their evolution. Intraocular antibody production and DNA was absent in the seven patients tested. In the present study, cerebrospinal and eye fluids culture and PCR as well as intrathecal immunoglobulin synthesis were also negative, which is not surprising, considering reports found in literature. PCR method is more sensitive for skin biopsies (64%) and synovial fluid (83%)¹⁶ than cerebrospinal (25%–38%)²¹ and ocular fluids (anecdotal case reports).²² Cerebrospinal serology has a good specificity (97%) but a lower sensitivity (75%) for detection of *Borrelia* antibodies in neuro-Lyme patients,¹⁹ while culture are almost always negative.¹⁶

Mikkila *et al* studying 161 uveitis in an endemic area of Finland found that 2.5% were association with Lyme disease, based on history of tick bites, systemic symptoms, response to antibiotherapy and/or positive PCR result. The authors recommended screening only for uveitis of unknown cause, especially in patients with vitritis or other symptoms of Lyme borreliosis.²³

In France, Salabert *et al* reported a comparative study on 104 patients divided in three groups: 34 unknown uveitis, 33 of known aetiology and 37 non-uveitis control patients. There was no significant difference in the seroprevalence for Lyme disease in all three groups (12.1%, 11.8% and 13.5%, respectively), showing the inefficiency of screening patients without history or additional symptoms.²⁴

A similar comparative study from the Netherlands²⁵ compared 56 consecutive patients of unknown origin with 56 uveitis of established aetiology and found a positive Lyme serology (two-tiered method) in 14% of the first group and 5% of the second (non-significant difference). Moreover, none of the seropositive patients fulfilled the CDC criteria for diagnosis of Lyme borreliosis. They concluded that Lyme is not a frequent cause of uveitis and initial screening is of very limited value.

In contrast to these European studies, 1 Japanese study of 2 endemic regions showed statistical difference in the seroprevalence of 94 unclassified uveitis compared with 84 healthy controls: 2.5% in Kanagawa, 37.7% in Hokkaido, for only 1.2% in the control group.¹⁵ However, this study did not specify which tests were performed to consider the uveitis as unclassified, and therefore cannot be compared with the others studies concerning first intention serological testing.

In our study, the pattern of uveitis related to a *Borrelia* infection was varied, including all anatomic localisations. Interestingly, all patients reported either a previous exposure including tick bite or forest walks, symptoms suggestive of Lyme disease and resistance to local and/or systemic steroids. Of importance, only 28.6% of patients can actually recall a tick bite, which makes history of exposure (forest walks in an endemic area) and physical symptoms of most importance in diagnosing Lyme disease.⁶

The limits of our study are that it is retrospective and that serological techniques and equipment have changed over the years, leading to possible inconsistencies in the interpretation of the results. Moreover, our patients were included in a tertiary centre which might not be representative of the general uveitis population. Finally, the screening for Lyme was not realised on all patients (either not at all or in another laboratory) so we could only include 430 of the 1006 patients.

In conclusion, our study, which is the second largest to date, confirms the low prevalence of Lyme disease and thus the low predictive value of serological testing. The risk of systematic screening is many false positives, leading to unnecessary antibiotic treatment and delaying correct diagnosis and treatment. Therefore serology should not be systematic, but always guided by an exposure history, systemic findings suggestive of Lyme disease and steroids resistance, in patients with unexplained uveitis. Indeed, clinical tailoring of serology is indispensable to carefully use the health economic resources of blood testing.

Contributors PS and LK were the principal investigators who conceived and designed the study. CR was the biologist retrieving data of the serological analyses. This manuscript was drafted by AB, revised by PS, LK, AA and AnB and read and approved by all living authors.

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