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Lyme arthritis is rare in Eastern Denmark

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ABSTRACT

INTRODUCTION The multi-organ disease Lyme borreliosis can cause mainly large joint arthritis. No guideline exists describing how to diagnose Lyme arthritis (LA). The incidence of LA in Denmark remains unknown, but it is considered to be low. The primary aim of this study was to quantify the number of *Borrelia burgdorferi* serological tests requested from primary and secondary care; secondly, to examine how often LA is diagnosed.

METHODS this was a register-based study including *B. burgdorferi* serological tests analysed at the department of clinical microbiology at Hvidovre and Herlev Hospitals during a two-year period. The results of the tests were categorised into primary and secondary care. A medical record review was made covering all newly referred rheumatological patients with *B. burgdorferi* serological tests analysed the Department of Clinical Microbiology, Hvidovre Hospital. A model was set up to diagnose LA.

RESULTS Most tests were requested by primary care. A total of 146 rheumatology patients were tested for *B. burgdorferi* of whom 118 were newly referred. Using our model to diagnose LA, we found that three patients had possible LA, whereas one had likely LA, but none were given a final LA diagnosis. Overdiagnosis was not common among rheumatologists.

CONCLUSION. The number of requested *B. burgdorferi* serological tests was highest in primary care. A clear guideline describing how to diagnose LA is needed in primary and secondary care alike.

FUNDING none.

TRIAL REGISTRATION Under current Danish law, no formal ethical approval was required for this study. Approval for this study was obtained from the Danish Data Protection Agency (no. 2012-58-0004).

Lyme borreliosis (LB) is a multi-system disease caused by the spirochete *Borrelia burgdorferi* sensu lato transmitted to humans by the tick *Ixodes ricinus*.

LB is the most frequent arthropod-borne infection in Europe with approximately 60,000 reported cases annually [1]. Incidence increases from west to east in Europe and a decreasing incidence have been observed from south to north in Scandinavia [2].

The clinical manifestations of LB are divided into three stages. The first stage, erythema migrans, affects the skin with a rash that spreads from the tick bite site. Dissemination to other organs is seen in stage 2 with early infection and in stage 3 with late infection [3, 4]. The manifestations of LB depend on the genetic difference between *B. burgdorferi* species. *B. burgdorferi* sensu stricto is often associated with Lyme arthritis (LA) [4].

LA is an intermittent or persistent mono- or oligoarthritis of the large joints, especially the knees [3]. LA is primarily seen as an early manifestation of disseminated LB, but it can also be seen as chronical arthritis as late

disseminated LB. It remains unknown whether the cause of LA is infectious or reactive [5]. LA is a leading manifestation of LB in the United States, where 60% of cases are affected by *B. burgdorferi* [3]. LA is rarely seen in Europe [6]. The incidence of LA in Denmark remains unknown [5], but it is considered to be low. Given the absence of definite diagnostic criteria and symptoms, the diagnosis of LA is difficult, and the objective findings are like those of other types of reactive arthritis [5]. Treatment for LA is therefore often initiated on suspicion of arthritis of the large joints combined with a history of exposure to *B. burgdorferi, e.g.* tick bite or erythema migrans. Positive immunoglobulin (Ig) G *B. burgdorferi* antibodies support the diagnosis [1, 5]. The diagnosis can be confirmed by polymerase chain reaction (PCR) on synovial fluid, but sensitivity to PCR varies greatly. *B. burgdorferi*-specific PCR is not performed routinely in Denmark [5].

LB is an often-considered diagnosis in Denmark with an estimated 75,000 required serological antibody tests annually [1]. Many serological tests for *B. burgdorferi* antibodies are required from general practice (GP) [7]. In this study, we selected patients diagnosed in rheumatological departments.

The aims of the study were to investigate how often a blood test for *B. burgdorferi* antibodies was requested from GPs and from hospitals. A second aim was to determine how often LA was diagnosed, how the diagnosis was made, and to evaluate whether the test results helped the rheumatologists in diagnosing LA.

METHODS

This was a register-based study.

Study population

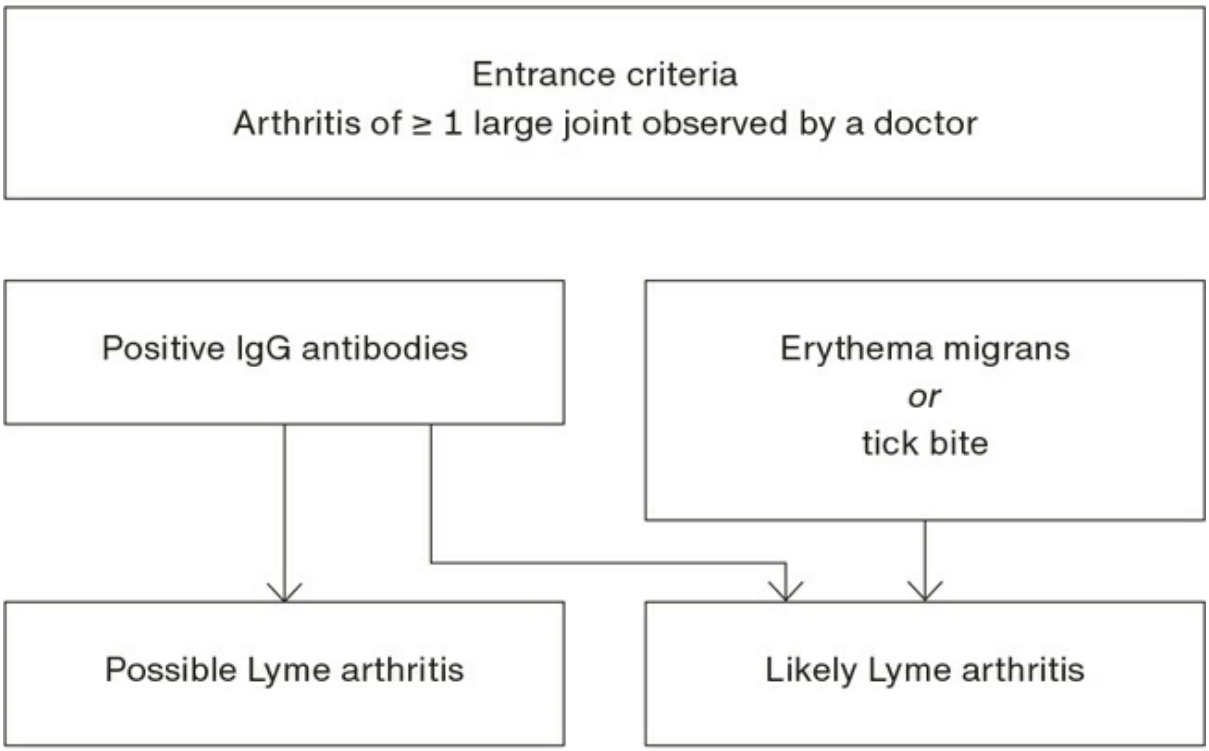
The study included all patients in the Capital Region of Denmark who had a blood sample analysed for *B. burgdorferi* antibodies (IgM and IgG) from 1 December 2012 to 30 November 2014. Blood samples were collected from patients by GPs and from patients in hospitals (outpatients as well as inpatients).

Among all patients who had a *B. burgdorferi* serologic test analysed in the Department of Clinical Microbiology, Hvidovre Hospital, a subgroup of patients whose test had been requested by a Department of Rheumatology, was singled out for special analysis. Among this group (146 patients in total), the medical records were reviewed for all newly referred patients (in total 118 patients – 21 inpatients and 97 outpatients).

The medical record was reviewed for any symptoms of LA and for the following details: referral diagnosis, medical history regarding tick bites, erythema migrans, arthralgia, swelling of joint, radiating pain, fatigue, fever, dizziness and prior treatment for Lyme disease. Furthermore, we registered if the physical examination revealed arthritis or dermatological changes related to Lyme disease. Finally, the definite diagnosis was recorded.

The symptoms were scored according to the model shown in **Figure 1** to determine the likelihood of LA.

FIGURE 1 Classification of Lyme arthritis.



Ig = immunoglobulin.

LA was classified as likely in case of registration of an objective swelling of ≥ 1 large joint, a history of thick bite or erythema migrans and positive *B. burgdorferi* IgG antibodies. LA was classified as possible if positive *B. burgdorferi* IgG antibodies were registered without a tick bite or erythema migrans.

Diagnostic assays

The blood samples were analysed in the Department of Clinical Microbiology, Hvidovre Hospital, and in the Department of Clinical Microbiology, Herlev Hospital. For detection of *B. burgdorferi* antibodies, two different assays were used: The Department of Clinical Microbiology, Herlev Hospital, used Liaison Borrelia IgM and Liaison Borrelia IgG (Diasorin S.p.a., Saluggia, Italy). The Department of Clinical Microbiology, Hvidovre Hospital, used Enzygnost Lyme link IgG/VlsE and Enzygnost Borreliosis/IgM (Siemens Healthcare Diagnostics GmbH, Marburg, Germany). Both assays were completed according to the manufacturer' s instructions

Trial registration: Under current Danish law, no formal ethical approval was required for this study. Approval of this study was obtained from The Danish Data Protection Agency (no. 2012-58-0004).

RESULTS

In total, 15,707 analyses for *B. burgdorferi* antibodies were performed in the Department of Clinical Microbiology, Hvidovre Hospital; 7,851 for IgG and 7,856 for IgM antibodies. The test results are presented in **Table 1.**

TABLE 1 Distribution of test results by ordering healthcare organisation for tests analysed at Hvidovre Hospital. The values are n (%).

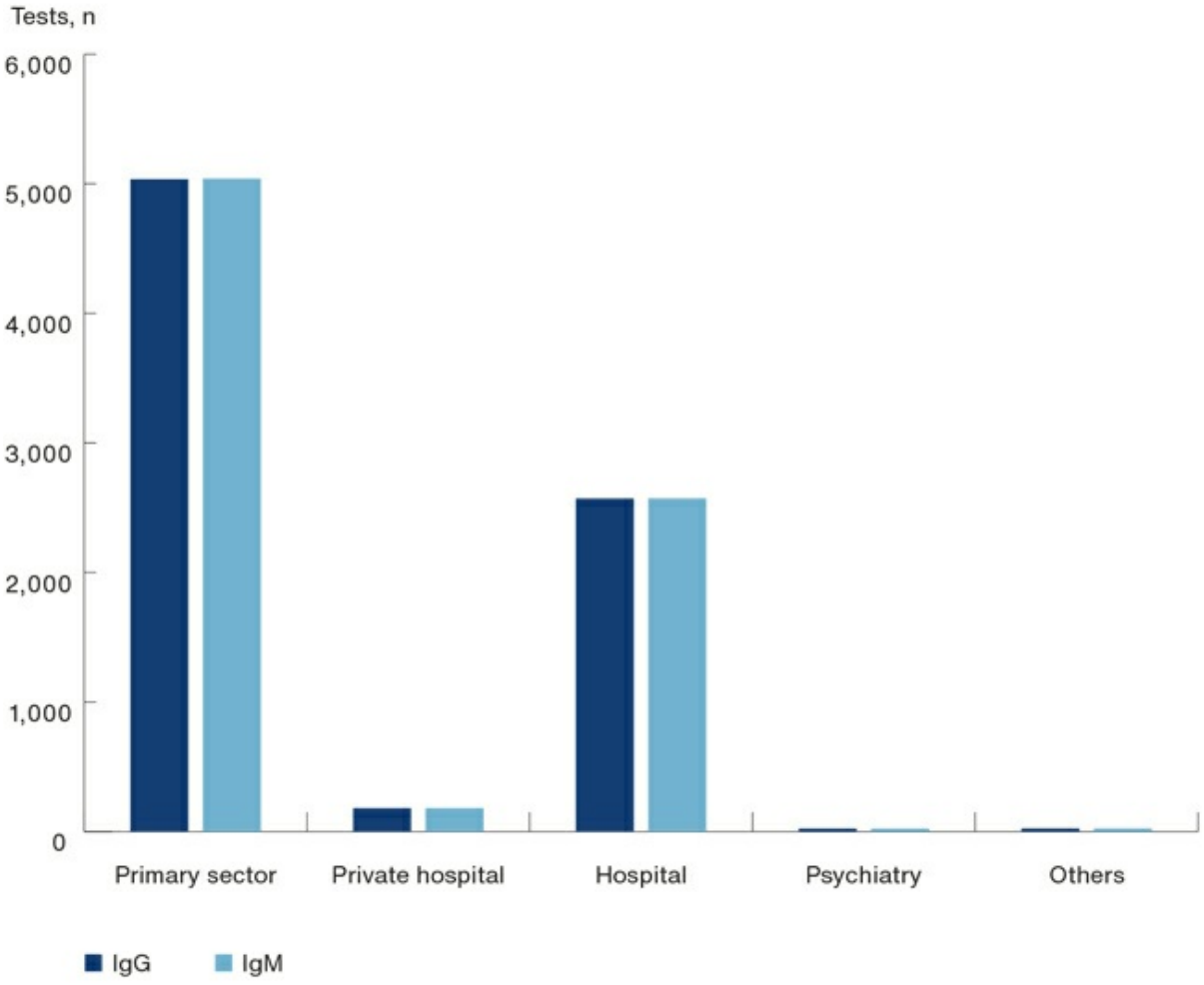
	IgG				IgM			
	negative	positive	equivocal	total	negative	positive	equivocal	total
Primary sector	4,212 (83.8)	661 (13.1)	162 (3.2)	5,035	4,220 (83.7)	606 (12.0)	213 (4.2)	5,039
Private hospitals	161 (88.5)	16 (8.8)	5 (2.7)	182	163 (89.6)	12 (6.6)	7 (3.8)	182
Psychiatry	19 (83.6)	3 (13.0)	1 (4.3)	23	20 (87.0)	2 (8.7)	1 (4.3)	23
Hospitals	2,230 (86.8)	288 (11.2)	52 (2.0)	2,570	2,261 (87.9)	200 (7.8)	110 (4.3)	2,571
Others	23 (92.0)	1 (4.0)	1 (4.0)	25	23 (92.0)	1 (4.0)	1 (4.0)	25

Ig = immunoglobulin.

Among the tested samples, 56% were from females and 44% were from males. The mean age was 47.8 years. A total of 733 patients were tested more than once. The majority, 586 patients, had two samples of *B. burgdorferi* antibodies taken. The highest number of samples taken from the same patient was nine IgM and eight IgG.

Figure 2 shows the distribution of *B. burgdorferi* IgG and IgM antibodies ordered by primary care (both GPs and specialised private clinics), psychiatric departments and private and public hospitals. Table 1 shows the results of the ordered tests.

FIGURE 2 Quantity of *Borrelia burgdorferi* serological tests distributed among requestors.



Ig = immunoglobulin.

In total, 27,979 analyses for *B. burgdorferi* antibodies were performed in the Department of Clinical Microbiology, Herlev Hospital, with 13,984 samples for IgG antibodies of which 11% (n = 1,545) were positive, 86.5% (n = 12,097) were negative and 2.4% (n = 342) were equivocal. Furthermore, a total of 13,999 samples were tested for IgM antibodies of which 13.6% (n = 1,911) were positive, 82.5% (n = 11,543) were negative and 3.9% (n = 539) were equivocal. Six analyses for IgM did not have a test result registered.

Results of clinical record review of the rheumatological patients

In total, 146 rheumatology patients were identified (mean age 47.35 ± 15.9 years). In total, 156 sets of *B. burgdorferi* IgM and IgG were ordered by a rheumatology department, among which 136 patients had one set taken and ten patients had two sets of samples taken. Out of the 146 patients, 118 patients (80.8%) had the sample taken as a part of the initial diagnostic procedure and were newly referred – 21 inpatients (17.8%) and 97 outpatients (82.2%). Fifteen (12.7%) were positive. Two patients (1.7%) had equivocal positive IgG antibodies, 11 patients (9.3%) were positive for IgM and seven patients were (5.9%) equivocal IgM. Review of the medical records of those patients showed that 18 patients (15.3%) had reported a previous thick bite and six (5.1%) had had erythema migrans. The registrations from the physical examinations showed that 34 (28.8%) patients had arthritis of a large joint. Among these 34 patients, three reported to have had a thick bite, two reported to have had erythema migrans and four patients had a positive IgG.

We used our model to evaluate if any newly referred patients with large joint arthritis had LA. Only one patient was found to have a likely LA and three to have possible LA. None of these four patients were described with the LA diagnosis in their medical records. Characteristics, symptoms and final diagnoses are shown in **Table 2.**

TABLE 2 Characteristics of patients with likely or possible Lyme arthritis using the classification model of Lyme arthritis.

Case no.	Sex	Age, yrs	Arthritis of	IgG-positive	Tick bite	Erythema migrans	Lyme arthritis	Final diagnosis
1	Female	55	Knee	+	-	+	Likely	Meniscal lesion
2	Female	24	Ankles	+	-	-	Possible	Sarcoidosis
3	Female	37	Wrist and finger joints	+	-	-	Possible	Morbus Still
4	Female	34	Ankle and finger joints	+	-	-	Possible	Arthritis unspecified

Ig = immunoglobulin.

Of interest, one patient had had a previous LA diagnosis, which had been made by a rheumatologist in a private clinic and the patient's symptoms improved after treatment. The patient was subsequently referred to a hospital department under the diagnosis of rheumatoid arthritis, but finally the arthritis diagnosis was disproved.

In total, two patients were referred under the LA diagnosis, but none of these patients were finally diagnosed with LA. One had the final diagnosis meniscal lesion, whereas the other patient was diagnosed with unspecified reactive arthritis. This patient had arthritis of the knee and elbow and had negative IgG antibodies twice.

DISCUSSION

The results showed that most samples were ordered by GPs. We were unable to calculate the test incidence. Besides, we did not examine which rheumatological diagnoses the GPs had considered. A previous Danish study revealed a large number of *B. burgdorferi* tests ordered by GPs with an annual LB test incidence of 267/100,000. The same study found that 38% of the samples ordered by GPs were due to suspected erythema migrans, 23% to arthritis and 13% to neurological symptoms [7]. Since only 60% of patients with erythema migrans will have developed *B. burgdorferi*-specific antibodies at the time of their diagnosis, laboratory tests are not recommended [4, 5]. Furthermore, the Danish study found that 44.9% of patients with a rash were treated with antibiotics even though only 17.2% of the detected *B. burgdorferi* were IgM positive and 4.7% were *B. burgdorferi* IgG positive. The background IgG seropositivity in Denmark is 2% [7].

In our study, based on test results from Hvidovre and Herlev Hospitals, we found an overall IgG seropositivity rate of 12.6% and 11% and an overall IgM seropositivity rate of 10.5% and 13.6%, respectively. These findings differ from the seropositivity rates found in the Danish study of tests ordered by GPs who reported a 3.3% IgG seropositivity and a 9.2% IgM seropositivity [7]. The seropositivity rates were generally higher in our study than in the previous Danish study, including the number of positive *B. burgdorferi* IgG antibodies in tests ordered by GPs (13.1%), psychiatry (13.0%) and hospitals (11.2%). In contrast, the IgM antibodies found in our study were more in line with those found in the previous Danish study (Table 1). One explanation for these findings may be that three different commercial assays were used in the two studies. In the previous Danish study, IgG and IgM were measured by Oxoid, Cambridge, UK [7], whereas, in the present study, we used Siemens Enzygnost Borreliosis/IgM, Siemens Enzygnost Lyme link VlsE/IgG and Liaison Borrelia IgG and IgM (Diasorin). The importance of this difference, however, has yet to be established.

In rheumatology, no clear guideline exists describing when to order *B. burgdorferi* serology. In our study, 146 rheumatology patients had serologically tests for *B. burgdorferi* performed within a two-year period. From the review of the medical records, a wide range of symptoms explained why *B. burgdorferi* serology had been ordered. The review revealed that the most frequent causes were arthritis and/or arthralgia (n = 34) and radiating back pain (n = 25), but also unspecific symptoms such as fever, fatigue and control after previous positive tests or tick bites triggered testing.

Two studies on the diagnostic usefulness of routine *B. burgdorferi* serology in patients with arthritis have been conducted in France. One of these studied patients with early inflammatory arthritis in a non-endemic area including 90 patients with inflammatory joint disease (both arthritis and arthralgia). Only one patient reported a tick bite, none reported erythema migrans and none had a positive *B. burgdorferi* serology [8]. Another French multicentre study included 810 patients with arthritis of ≥ 2 joints. *B. burgdorferi* serology was performed at baseline with results kept unavailable to the physician, who therefore independently had to order *B. burgdorferi* serology if LA was suspected. In total, 7.6% were *B. burgdorferi* IgG positive and the possibility of LA could therefore not be excluded. LA was suspected in two cases, both had negative *B. burgdorferi* serology and another diagnosis was given [9]. Of note, this study excluded patients with monoarthritis, which is the most typical manifestation of LA.

Supported by the Danish LB Clarification Report from 2014 [5], we set up a model to evaluate if LA was likely or possible in the cases included in our study. This model revealed only a few cases in which LA is likely or possible, but only one of these patients was given the final diagnosis of non-specific arthritis and this patient thus had a possible LA. Our model resembles the diagnostic approach recommended in the American review on diagnosis and treatment of LA. The American approach established that the patients might not recall a tick bite or erythema migrans, for which reason staying in a high endemic area musts also be taken into consideration [10]. In our study, two cases had *B. burgdorferi* serology taken due to a stay in Sweden where the incidence of *B. burgdorferi* is higher than in Denmark. We defined arthritis of ≥ 1 large joint as an inclusion criterion. If a patient had arthritis of at least one large joint and also had arthritis of small joints, they were included as well even though the typical manifestation is large joint arthritis [4]. Two of the patients with possible LA also had arthritis of finger joints. The fact that we included only patients with arthritis of at least one large joint may have meant that some possible cases of LA were overlooked. The American review stated that in the early phase of LA in particular, small joints may be affected [10].

CONCLUSION

Most *B. burgdorferi* tests were requested by GPs. *B. burgdorferi* serology was used in the initial rheumatological

diagnostics of patients with a wide range of symptoms, especially arthritis, arthralgia and radiating back pain. LA was often considered by rheumatologists, but the diagnosis was never given. This indicates that overdiagnosis of LA is not a problem in Denmark and that LA is a rare diagnosis. A clearly defined diagnosis of LA does not exist.

Use of our classification model for LA established only one case of possible LA. Based on the results of the study, the authors see a need for guidelines describing how to diagnose LA and how to interpretate the serological tests. Further studies of the usefulness of *B. burgdorferi* serology in diagnostics of rheumatology patients are warranted both for primary and secondary care.

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