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CASE BASED REVIEW

Differentiating Lyme arthritis: a case-based review

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Abstract

The incidence or prevalence of Lyme arthritis (LA) in Denmark is unknown and assumed very low. No published cases of polymerase chain reaction (PCR)-confirmed LA from Denmark exist. Clinically, LA does not differ from other rheumatic oligoarthritic disorders posing a differential diagnostic challenge. To review the incidence and prevalence of LA to our knowledge and to present a case series of PCR-confirmed LA cases from Denmark. We conducted a systematic literature review via MEDLINE and EMBASE to explore incidence and prevalence rates of LA. Additionally, we present six cases of patients diagnosed with LA in Denmark. Our literature review identified 23 studies reporting prevalence or incidence, yet only ten studies provided estimates ranging from 1.1 to 280/100.000 in the general population. Our case series identified six patients with LA from a localized region in Southern Denmark; all confirmed by *Borrelia*-specific real-time PCR from synovial fluid. The diagnostic delay was up to 38 months. All patients except one had a history of previous tick bites; none had erythema migrans lesions. All presented with recurrent arthritis in the knee joint, and two had arthritis in the wrist. The literature review showed an incidence of LA ranging from 1.1 to 15.8 per 100.000 in Europe. Our case series suggests a potentially higher prevalence of LA in Denmark than previously believed. Lack of tick exposure history, antibody assessments and test of *Borrelia burgdorferi* sensu lato DNA in synovial fluid might lead to misdiagnosed cases potentially explaining the assumed low incidence of LA in Denmark.

Keywords *Borrelia burgdorferi* sensu lato · Arthritis, infectious · Lyme disease · Europe · Case reports

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Introduction

Lyme borreliosis (LB), caused by bacteria within the *Borrelia burgdorferi* sensu lato (*B.b*.s.l) complex, is the most common tick-borne disease in Europe and North America, exhibiting a wide range of clinical manifestations. Depending on the involved *B.b*.s.l genospecies, symptoms can affect various organ systems, including skin, nervous system, heart, and joints [1–5].

Lyme arthritis (LA) is mainly caused by *Borrelia burgdorferi* sensu stricto (*B.b*.s.s), which is the predominant pathogenic *Borrelia* species in North America [2, 4]. Conversely, *Borrelia garinii* (*B. garinii*) and *Borrelia afzelii* (*B. afzelii*) *are* considered the most prevalent species in Europe [6]. However, data on the incidence and prevalence of LA remains scarce, particularly in Denmark, where both incidence and prevalence are presumed very low. To our knowledge, no published cases of LA in Denmark confirmed by real-time polymerase chain reaction (PCR) exists.

In the following, we describe a case series of LA originating from a specific region in Southern Denmark, preceded by a systematic literature review in Medline and EMBASE of the incidence and prevalence of LA. The aim of this case-based review is to highlight the significance of considering LA as differential diagnosis in the assessment of patients with mono – and oligoarthritis. Further, we aim for summarizing the current knowledge concerning the incidence and prevalence of LA.

Methods

The systematic review

We conducted a systematic search of the literature using MEDLINE (via PubMed) and EMBASE (via OVID) databases from November 05 – 04, 2024, to identify studies on incidence or prevalence of LA. Our search strategy combined words including Lyme arthritis, prevalence, and incidence (the search strategy is detailed outlined in Appendix A). We included only studies limited to human studies, published in English as full-text papers, with no limits on year of publication.

The case series

The first LA case was identified in August 2021 at the Department of Rheumatology, University Hospital of Southern Denmark, Esbjerg, Denmark. In total, six cases were registered until February 2023. The diagnoses were confirmed by the detection of *B.b*.s.l. DNA by real-time PCR at the Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark, as described by Leth et al. 2023 [7].

Results

Search results and characteristics of studies

Based on the title and abstract, our literature research identified 1,611 records. Removal of duplicates left 932 records that were retrieved and evaluated accordingly (Fig. 1). 872 records were excluded due to lack of information concerning incidence or prevalence, and 15 studies were excluded as they were published only as conference abstracts without full-text publication. Finally, 22 studies were excluded, as they did not report on human, leaving 23 studies for a complete evaluation.

Table 1 provides a summary of the included studies. Of these, 5 studies originated from the US (United States), while 18 studies were carried out across 8 European countries, predominantly Germany, Sweden and Poland. The studies showed significant heterogeneity and varied considerably in design and populations being investigated. Of the included studies, 13 were retrospective, eight were prospective, and two were reviews—only ten of the included studies allowed estimates of incidence or prevalence in the general population, as depicted in Table 2.

In the US, only three different studies allowed incidence and prevalence rate estimates. One study from 1977 reported an overall prevalence rate of LA at 4.3 cases/1,000 residents in three contiguous Connecticut communities [8], while another study from 1978 reported the incidence to range between 0.1 and 2.8/1000 residents depending on the investigated geographical area [9]. Finally, the average incidence of LA from high-incidence regions in the US yielded a calculated rate of 1.1/100,000 residents between 2005 and 2014 [10]. In Europe, only seven studies permitted estimations of incidence or prevalence rates within the general population. Among these, a Swedish study reported a prevalence of 2.3% in a high endemic population for LB in South Sweden [11] and another Swedish study reported an annual incidence of 2.0/100,000 residents in Kronoberg country in Southern Sweden [12]. A study from Norway estimated an annual incidence of 2.7/100,000 residents in Southern Norway [13], a study from Belgium outlined an incidence of 2.1/100,000 residents [14], and a recent study from Poland identified an annual incidence of 15.8/100,000 [15] residents. Furthermore, in a study conducted in an endemic area of Germany, the annual incidence of LA among individuals under 17 years old was documented to be 4/100,000 [16]. A recent study from Germany report an incidence of 7.4/100,000 in 2016 [17].

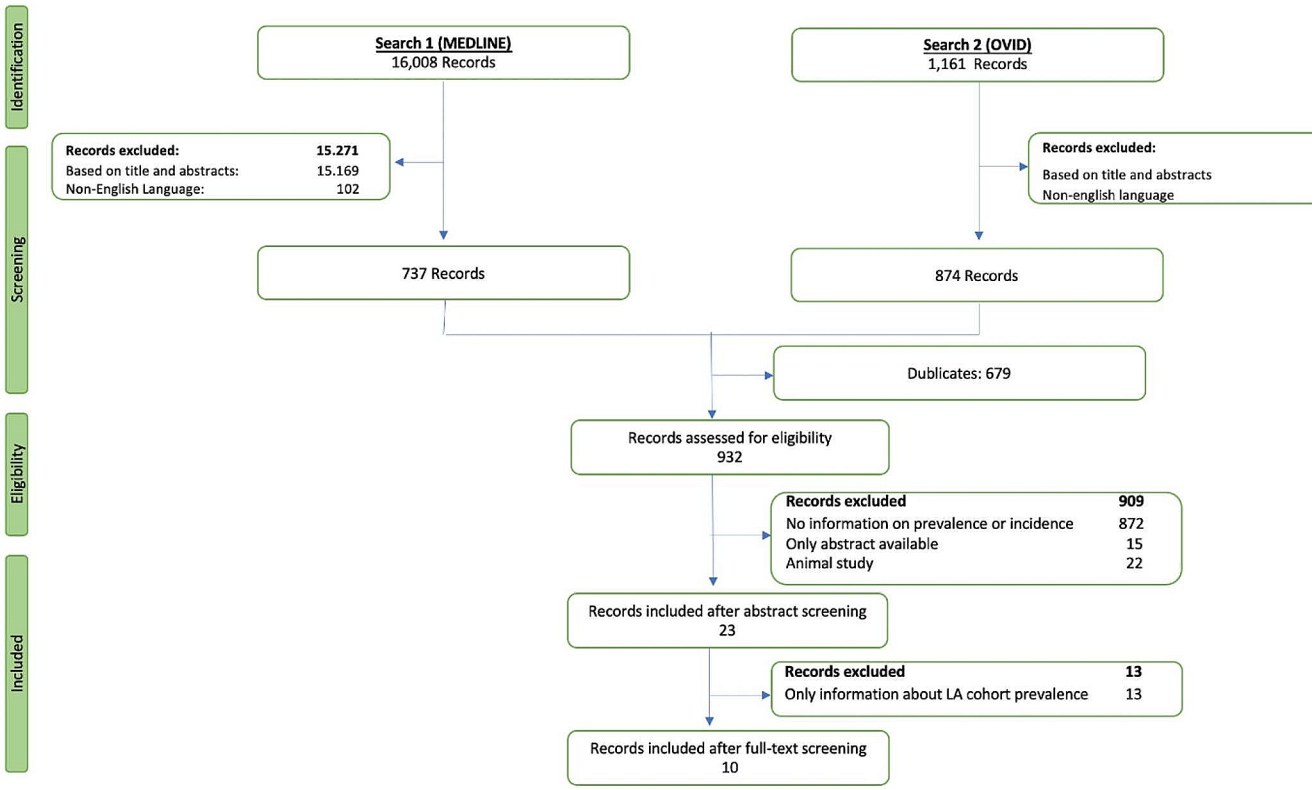

Fig. 1 Flowchart of Study idenfication, Inclusion, and Exclusion

The remaining studies did not allow estimates of incidence or prevalence rates in the general population. However, the studies did report a prevalence of the cohort being investigated ranging from 0 to 54% (Table 1).

Case presentations

In the following section, we present a case series comprising six patients with LA diagnosed at the Department of Rheumatology in Esbjerg, Denmark. All cases were confirmed by detection of *B.b*.s.l. DNA in synovial fluid by real-time PCR. Notably, all patients share a common interest in walking amidst nature within a small geographic area in Southern Denmark, a few kilometres north of the city of Esbjerg. None of the presented clinical cases exhibited systemic manifestations, a history of trauma, preexisting infections, or psoriasis.

Synovial fluid analysis revealed an absence of crystals, and both Gram stain and cultures produced negative results. Serological assessments, including rheumatoid factor and anticitrullinated peptides were negative across all cases. C-reactive protein (CRP) levels varied among the cases, and X-ray examinations did not reveal any signs of erosions. All cases displayed an excessive amount of synovial fluid. Muscular-skeletal ultrasound examinations demonstrated a high proliferation of synovium. A comprehensive overview of the clinical characteristics can be found in Table 3.

According to the Centers for Disease Control and Prevention (CDC) the current treatment recommendations for LA is a 4-week oral antibiotics regimen consisting of either doxycycline, amoxicillin, or cefuroxime. For patients who shows no response after the initial course of antibiotics, intravenous ceftriaxone is preferred regimen for second course of antibiotics [18]. In the first 3 cases, the patients received the intravenous treatment as first line of treatment because of the extensive diagnostic delay.

Case I

A 78-year-old man with the comorbidities of hypertension and diabetes was referred with recurrent mono-arthritis of the right knee in August 2018. The patient was treated with frequent intra-articular steroid injections. In August 2021, the medical history and test results were reviewed due to frequent contact over the past three years. LA was suspected due to positive serology for *B.b*.s.l. specific IgG antibodies and *Borrelia* DNA detected by PCR in synovial fluid in 2018; yet he had never received treatment. *B.b*.s.l. DNA was detected by PCR in a new synovial fluid sample in 2021. Treatment was initiated with intravenous ceftriaxone 2 g daily for 28 days, resulting in resolved joint swelling.

Table 1 Overview of studies from the literature research on the incidence and prevalence of Lyme arthritis including studies reporting cohort prevalences

No	Author	Year	Country	Study design	Cohort Prevalence	Incidence	Prevalence
1	Steere A.C. et al. [8]	1977	USA	Retrospective	0.43% (51/11.900)	n.a.	4.3/1.000[#]
2	Steere A.C. et al. [9]	1978	USA	Retrospective	45% (17/38)	2.8/1.000 (east side)[##] 0.1/1.000 (west side)[##]	n.a.
3	Herzer [22]	1991	Germany	Review	54.2% (65/120)	n.a.	n.a.
4	Huppertz HI et al. [16]	1995	Germany	Prospective	n.a.	4/100.000[*]	n.a.
5	Berglund J. et al. [11].	1995	Sweden	Prospective	35% (11/32)	n.a.	2.3%[**]
6	Berglund J. et al. [29].	1996	Sweden	Prospective	5% (5/100)	n.a.	n.a.
7	Huppertz HI et al. [30]	1999	Germany	Prospective	4.8% (15/313)	n.a.	n.a.
8	Söderlin MK [12]	2002	Sweden	Prospective	2% (3/151)	2/100.000	n.a.
9	Christova I et al. [31].	2004	Bulgaria	Retrospective	8% (101/1257)	n.a.	n.a.
10	Milewski M.D et al. [23].	2011	USA	Retrospective	31% (123/391)	7 cases per year[***]	n.a.
11	Moniuszko A. et al. [32]	2014	Poland	Retrospective	11.7% (32/273) - hip 25% (12/48) - knee	n.a.	n.a.
12	Wilking H et al. [33].	2014	Germany	Retrospective	2% (367/18.894)	n.a.	n.a.
13	Haugeberg et al. [13]	2014	Norway	Prospective	77.8% (21/27)	2.7/100.000	n.a.
14	Czupryna P et al. [34]	2016	Poland	Retrospective	2% (4/193)	n.a.	n.a.
15	Enkelmann J et al. [35].	2018	Germany	Retrospective	2.1% (1182/56.446)	n.a.	n.a.
16	Kwit NA et al. [10].	2018	USA	Prospective	2.8% (2440/88.022)	1.1/100.000	n.a.
17	Geebelen L et al. [14].	2019	Belgium	Systematic review/meta-analysis	n.a.	2.1/100.000	n.a.
18	Petrulioniene A [24]	2021	Lithuania	Retrospective	3.2% (32/1005)	n.a.	n.a.
19	Müller T et al. [19].	2021	Denmark	Retrospective	None	n.a.	n.a.
20	Sundheim KM et al. [36].	2021	USA	Prospective	53.1% (366/690)	n.a	n.a.
21	Böhmer MM et al. [37].	2021	Germany	Retrospective	1.8% (633/35.458)	n.a.	n.a.
22	Paradowska-Stankiewicz I et al. [15]	2023	Poland	Retrospective	32% (30.330/94.715)	15.8/100.000	n.a.
23	Brestrich et al. [17]	2024	Germany	Retrospective	2.9% (6.110/206.223)	7.4/100.000	n.a.

Abbreviations No (number), n.a. (not available), [#] (prevalence rate in three contiguous Connecticut communities), [##] (incident rate in three communities on the east side of the Connecticut River and nine on the west side), [*] (incidence in persons < 17 year), [**] (prevalence of LA in high endemic population for Lyme borreliosis in South Sweden), [***] (mean incidence in the study population)

Table 2 Overview of studies from the literature research on the incidence and prevalence of Lyme arthritis in the general population

No	Author	Year	Country	Study design	Cohort Prevalence	Incidence	Prevalence
1	Steere A.C. et al. [8]	1977	USA	Retrospective	0.43% (51/11.900)	n.a.	4.3/1.000[#]
2	Steere A.C. et al. [9]	1978	USA	Retrospective	45% (17/38)	2.8/1.000 (east side)[##] 0.1/1.000 (west side)[##]	n.a.
3	Huppertz HI et al. [16]	1995	Germany	Prospective	n.a.	4/100.000[*]	n.a.
4	Berglund J. et al. [11]	1995	Sweden	Prospective	35% (11/32)	n.a.	2.3%[**]
5	Söderlin MK [12]	2002	Sweden	Prospective	2% (3/151)	2/100.000	n.a.
6	Haugeberg et al. [13]	2014	Norway	Prospective	77.8% (21/27)	2.7/100.000	n.a.
7	Kwit NA et al. [10].	2018	USA	Prospective	2.8% (2440/88.022)	1.1/100.000	n.a.
8	Geebelen L et al. [14].	2019	Belgium	Systematic review	n.a.	2.1/100.000	n.a.
9	Paradowska-Stankiewicz I et al. [15]	2023	Poland	Retrospective	32% (30.330/94.715)	15.8/100.000	n.a.
10	Brestrich et al. [17]	2024	Germany	Retrospective	2.9% (6.110/206.223)	7.4/100.000	n.a.

Abbreviations No (number), n.a. (not available), [#] (prevalence rate in three contiguous Connecticut communities), [##] (incident rate in three communities on the east side of the Connecticut River and nine on the west side), [*] (incidence in persons < 17 year), [**](prevalence of LA in high endemic population for Lyme borreliosis in South Sweden)

Table 3 Main characteristic of patients included in case series

Sex	Age	Joint Affected	History of tick bite	History of Erythema migrans	B. burgdorferi IgG (serum)	B. burgdorferi IgM (serum)	B. burgdorferi PCR (synovial fluid)	C-reactive protein (mg/ml)	Symptom duration before diagnosis (mo*)	I.A steroid injection before AB	Treatment
Male I	78	Right Knee Right Wrist	Y	N	+	+	+	36	38	Frequent	Ceftriaxone (2 courses)
Male II	41	Left Knee Right Wrist	Y	N	+	+	+	105	14	Frequent	Ceftriaxone MTX
Male III	69	Right Knee	N	N	+	+	+	36	10	Frequent	Ceftriaxone
Male IV	78	Right Knee	Y	N	+	_	+	2	3	Two times	Doxycycline
Male V	32	Right Knee	Y	N	+	_	+	12	6	Frequent	Doxycycline Ceftriaxone MTX
Male VI	74	Left Knee	Y	N	+	+	+	67	2	Two times	Doxycycline Ceftriaxone MTX

Abbreviations Mo* (months), I.A (intra articular), AB (antibiotics), MTX (methotrexate), Y (yes), N (no), + (positive), - (negative)

However, one month later, he presented with arthritis in the right wrist. Arthrocentesis was performed, and *B.b*.s.l DNA was also detected in synovial fluid from this joint. An additional four-week course of intravenous ceftriaxone was conducted. Currently, he has been without joint symptoms for three years.

Case II

A 41-year-old man with no comorbidity was referred with persisting bilateral joint swelling of the knees in the spring of 2021. Sulfasalazine was prescribed. Due to persisting arthritis, oral methotrexate (MTX) 20 mg was added. Within a month, arthritis developed in the right wrist. MTX was terminated due to intolerance. Throughout the fall of 2021, the patient received multiple steroid injections due to recurrent knee swelling. A synovectomy of the left knee was performed. However, one month later the swelling recurred. In January 2022 the medical history was reviewed, and LA was suspected based on previous tick bite exposure history. Serum tests revealed *B.b*.s.l. specific IgM and IgG antibodies, *B.b*.s.l. DNA was detected by PCR in synovial fluid from the left knee. Intravenous ceftriaxone for 28 days was initiated. Subsequently, he had persistent knee arthritis, and MTX treatment was resumed as subcutaneous injections. Currently, he has been without recurrent arthritis symptoms for 12 months.

Case III

A 69-year-old man with osteoarthritis was referred due to recurrent knee swelling in the early Spring of 2021. He was treated with frequent steroid injections with short-term effects. In March 2022, LA was suspected based on the two previously described cases. He had no recall of tick bites nor any skin rash. Serum tests revealed *B.b*.s.l. specific IgM and IgG antibodies, and *B.b*.s.l. DNA was detected by PCR in synovial fluid from the right knee. He was treated with a 4-week course of intravenous ceftriaxone with a complete improvement of symptoms. Currently, he has been without symptoms for 16 months.

Case IV

A 78-year-old man with hypertension, chronic kidney insufficiency, osteoarthrosis in the hips, and metastatic cancer ventriculi was referred in the Summer of 2022 due to recurrent arthritis of the right knee. He was treated with two intraarticular steroid injections with only short-term effects. At the second visit, he reported previous tick bites but denied any skin rash. Serum tests showed *B.b*.s.l. specific IgM and IgG antibodies, and *B.b*.s.l. DNA was detected by PCR in synovial fluid from the right knee. He received treatment with doxycycline for three weeks. No recurrence of arthritis has been seen to date.

Case V

A 32-year-old man with no comorbidities was referred in the Summer 2022 due to recurrent arthritis of the right knee. Similar to the previous cases the patient received frequent steroid injections, offering only short-term relief. The diagnosis of LA was given based on *B.b*.s.l. specific IgG antibodies, and *B.b*.s.l. DNA detected by PCR in synovial fluid from the right knee. The patient was treated with doxycycline, but due to the recurrence of arthritis, the patient was retreated with intravenous ceftriaxone. Afterward, he was

given MTX, but in August 2023 MTX was stopped due to remission. No recurrence of arthritis has been seen to date.

Case VI

A 74-year-old man with no comorbidities was referred in Winter 2023 due to recurrent arthritis of the left knee. The patient was treated two times with steroid injections offering only short-term relief. The diagnosis of LA was given based on results *B.b.*s.l. specific IgG antibodies, and *B.b.*s.l. DNA detected by PCR in synovial fluid from the left knee. The patient was first treated with doxycycline, but due to a recurrence of arthritis, he was retreated with intravenous ceftriaxone. Afterward, he was prescribed MTX, which he is currently taking. No recurrence of arthritis has been seen to date.

Discussion

Our literature review of Medline and EMBASE indicates a paucity of data on the incidence and prevalence of LA, yet LA exhibits modest but relatively equal incidence rates across different populations worldwide ranging from 1,1 to 15,8 per 100.000 excluding the 2 reports by Steere et al. from the US. The high incidence and prevalence rate of LA reported by Steere et al. in 1977–1978 raises concerns, emphasizing the potential impact of evolving diagnostic methods, treatment and awareness on the rates over time. Excluding those reports, our findings suggest an equal cohort prevalence of LA in US populations compared to Europe, where reported prevalence in various cohorts ranges considerably. Our review encompasses studies from eight European countries with highest incident rate in Poland. Some of the studies suggested that the incidence of LA might have been underestimated [13, 16].

Through our literature review, three studies in Denmark regarding the incidence or prevalence of LA were identified. One study reported no cases of LA [19]. Another study highlighted 1072 cases where LA could not be ruled out based on clinical features. Yet only 2.3% had IgG antibodies against *B.b.*s.l., similar to the Danish population's seropositivity rate. This led to the conclusion that LA was not apparent [19, 20]. Lastly, a Danish prospective study investigated the diagnostic outcomes and clinical characteristics of 215 adults referred to the Clinic for Tick-borne Diseases in Copenhagen. Only two patients displayed probable LA based on clinical presentation and high serum levels of IgG antibodies against *B.b.*s.l. However, synovial fluid was not obtained or examined for *B.b.*s.l. DNA. Both patients were treated presumptively for LA, but their recovery status was not specified [21].

This case series underscores the importance of considering LA when evaluating recurring mono- or oligo-arthritis, especially in the knee joints [8, 16]. This observation remains valid even in regions like Denmark, where LA is thought to be uncommon. Despite the limited number of cases and research on LA in Denmark [19], the series suggests a potential higher incidence and prevalence than previously believed. LA was not initially suspected in all instances, but our findings revealed a reduction in diagnostic delay with increased awareness. The first patient was diagnosed after 38 months, compared to 1.5 months in the most recent case. None of our patients had a history of EM, making this an unreliable factor in excluding LA, as observed in neuroborreliosis [25].

All patients resided in the same geographic area of Southern Denmark. It could be speculated that all cases may have had tick bites in this area, suggesting a new hotspot. Further studies on ticks in this region are essential, as the occurrence of *B.b.*s.s., which is not widespread in Denmark, may be high in ticks in this specific geographic area. Previous tick studies in Denmark have identified various *Borrelia* genospecies, with *B.b.*s.s. documented but at a lower prevalence than other genospecies. One study highlighted *B. afzelii* as the most common *Borrelia* genospecies in Danish ticks, followed by *B. valaisiana*, *B.b.*s.s., and *B. garinii* [26]. Similarly, other studies have shown that *B. afzelii* is a common genospecies [27, 28].

Lack of routine assessment of tick risk behaviour, antibody status, or evaluation of the presence of *B.b.*s.l DNA in synovial fluid by PCR can lead to undiagnosed cases. It's plausible that the relatively low incidence of LA in Denmark might be attributed partly to diminished consideration of *B.b.*s.l. as a potential cause for mono- or oligo-arthritis, given the absence of routine assessments for LA. Inadequate examinations might lead to an erroneously perceived low incidence. Our case series strongly advocates for heightened consideration of LA as a plausible differential diagnosis. Efforts to enhance diagnostic facilities should be prioritized to address these diagnostic challenges.

Limitations

Firstly, excluding studies solely published as conference abstracts may result in the omission of potentially pertinent data. Secondly, excluding non-English literature also carries the risk of overlooking relevant information. Lastly, our case series comprises only a limited number of cases from a narrowly defined area in Southern Denmark, thus constraining the generalizability of our findings.

Conclusion

This case series underscores the importance of considering LA as a crucial differential diagnosis in patients with persistent or intermittent mono- or oligo-arthritis, despite its perceived low incidence and prevalence in Denmark. While our systematic literature review of Medline and EMBASE indicates limited knowledge understanding of LA incidence and prevalence, it highlights its presence across various countries, with rates varying depending on the studied population. Our case series demonstrates a significant reduction in diagnostic delay when clinicians consider LA as a potential explanation for arthritis symptoms. Further research is urgently needed to elucidate the magnitude of this issue, both on a broader scale and within specific regions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-024-05618-0.

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Author contributions Ayse Mine Unlu and Philip Rask Lage-Hansen contributed to the study's conception and design. Ayse Mine Unlu conducted the systematic literature search, screened the retrieved records, and created the flowchart and table. Ayse Mine Unlu and Philip Rask Lage-Hansen drafted the initial manuscript. Clinicians (Nanna Skaarup Andersen and Sanne Løkkegaard Larsen) from the Department of Clinical Microbiology described and conducted the *B.b.*s.l. specific PCR analyses. Philip Rask Lage-Hansen and Stavros Chrysidis diagnosed the patients in this case series, with Sigurdur Skarphedinsson consulted regarding antibiotic treatment in all cases. All authors critically reviewed and contributed substantially to the manuscript's refinement. All authors take full responsibility for the integrity and accuracy of all aspects of the work.

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Declarations

Ethical approval In accordance with Danish national regulations, case reports are not subject to approval by any ethics committee. Written informed consent was obtained from all patients for publication of data pertaining to their medical history and laboratory test results.

Conflict of interest The authors declare no conflict of interest.

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