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Diagnostic impact of routine Lyme serology in recent-onset arthritis: results from the ESPOIR cohort

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ABSTRACT

Objectives: Lyme disease may be considered by rheumatologists in patients with recent-onset arthritis, even in the absence of suggestive symptoms. The aim of this study was to determine the diagnostic impact of routine Lyme serology in a French cohort of patients with recent-onset arthritis affecting at least 2 joints.

Methods: We performed an ancillary study of a French prospective multicentre cohort established to monitor clinical, biological and radiographic data in patients with inflammatory arthritis in at least 2 joints, lasting for 6 weeks to 6 months. *Borrelia* IgM and IgG antibodies were sought routinely at baseline, using ELISA tests, independently from the physician's strategy for detecting a spirochetal infection. We recorded the proportion of patients with a final diagnosis of Lyme arthritis and evaluated the diagnostic performance of Lyme serology in this particular context. The clinical and biological characteristics of patients according to the Lyme serology results were analysed.

Results: Of 810 patients, 657 (81.1%) were negative for IgM and IgG antibodies, 91 (11.2%) had only IgM antibodies, 49 (6%) had only IgG antibodies, and 13 (1.6%) had IgG and IgM antibodies. Thus, 7.6% had IgG positivity, consistent with exposure to *Borrelia infection*. IgG positivity was significantly more prevalent in the North and North-East regions of France ($\chi^2=14.6$, $p<0.001$). No patients received a definite diagnosis of Lyme arthritis.

Conclusions: This study does not support routine Lyme serological testing in patients with recent-onset inflammatory arthritis affecting more than 1 joint.

INTRODUCTION

Lyme disease is an infection due to the spirochete *Borrelia* and spreads to humans by infected *Ixodes* ticks. It is the most common arthropod-borne disease in temperate regions of the northern hemisphere. In the USA, *Borrelia burgdorferi sensu stricto* is the only species responsible for Lyme disease.

Key messages**What is already known on this subject?**

► Lyme serology is not recommended as a routine test in patients with recent-onset arthritis affecting more than one joint but some rheumatologists prescribe it in this context.

What does this study add?

► This study confirms that more than 10% of patients with recent-onset arthritis not due to Lyme disease have positive Lyme serological tests.

How might this impact on clinical practice?

► Routine Lyme serology is unnecessary in this context.

In Europe and Asia, the disease can be due to at least two additional genospecies: *Borrelia afzelii* and *Borrelia garinii*. All genospecies known to cause Lyme disease are regrouped in the *Borrelia burgdorferi sensu lato* complex. Risk factors for Lyme disease include occupational and recreational activities in grassy or wooded areas.¹ In Europe, incidence rates range across countries from less than 1/100 000 (England, Portugal and Turkey) to about 350/100 000 population (Austria).² In France, the disease occurs in all regions except the Mediterranean rim and high mountains, with an overall annual incidence estimated at 16/100 000 population and several endemic areas, such as Alsace, where the incidence reaches 250/100 000 population.³

Erythema migrans (EM) is the most common manifestation of Lyme disease. It begins 2–32 days after the bite as a red macule and expands over days to weeks to an erythematous annular lesion of 5 cm to greater than 68 cm. It may be accompanied with a flu-like syndrome. EM is typical but



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may be absent or missed in 20–30% of cases, delaying the diagnosis of Lyme disease until the infection disseminates into other organs.⁴ Several weeks or months after the inoculation, untreated patients may experience systemic manifestations such as neuroborreliosis (meningoradiculitis, meningitis or meningoencephalitis), arthritis or *Borrelia* lymphocytoma. Multiple EM lesions and cardiac manifestations are less common. Months to years after the inoculation, acrodermatitis chronica atrophicans, lymphocytoma, chronic arthritis, encephalomyelitis or chronic neuroborreliosis may develop.^{2 5}

During the early stages of Lyme disease, non-specific arthralgia may occur in up to 70% of cases. Lyme arthritis may develop at the early or late stage of dissemination. The typical presentation, concerning more than 90% of patients with Lyme arthritis, is relapsing/remitting monoarthritis or oligoarthritis that chiefly affects the large joints, most notably the knee. Other rare presentations such as polyarthritis and polyarthralgia have been reported in up to 6% of cases.⁶ Joint erosions have been observed in some patients with longstanding untreated infection or antibiotic-unresponsive disease.⁷ In cases of suspected Lyme arthritis, it is recommended to perform an ELISA test and to confirm it by a Western blot test. High levels of IgG antibodies are usually detected. Synovial fluid/tissue culture and PCR are optional.

To date, Lyme serology is not recommended as a routine test in patients with recent-onset arthritis affecting more than one joint and lasting for several weeks. However, rheumatologists sometimes consider Lyme arthritis as a differential diagnosis in this group of patients, even in non-endemic regions and in the absence of typical articular manifestations or extra-articular symptoms.⁸ Given the high proportion of *Borrelia*-infected patients who do not develop EM, the increasing incidence of Lyme disease in several areas, as well as the broad spectrum of the joint manifestations of Lyme arthritis and the diagnostic usefulness of routine Lyme serology in patients with recent-onset arthritis, deserves investigation.

Here, our aim was to determine the diagnostic usefulness of routine Lyme serology in a French cohort of patients with recent-onset arthritis affecting more than one joint. We evaluated the prevalence of *Borrelia* antibodies in each geographic region, the prevalence of Lyme arthritis and the diagnostic accuracy of Lyme serology. We also assessed whether Lyme serology results were influenced by clinical or biological parameters related to the inflammatory arthritis or general health status.

METHODS

Study population

We conducted an ancillary study of data from the French prospective multicentre ESPOIR cohort established to monitor clinical, biological and radiographic

data from patients with recent-onset inflammatory arthritis affecting more than one joint. General practitioners and rheumatologists referred patients to 14 centres in 10 regions throughout France. Patient inclusion occurred from December 2002 to March 2005.⁹

Patients were eligible if they were 18–70 years of age and had either a definitive or probable clinical diagnosis of rheumatoid arthritis or polyarthritis not better explained by another aetiology. Additional inclusion criteria were swelling of at least two joints for 6 weeks to 6 months and no prior treatment with disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids; however, glucocorticoid therapy in a mean dosage ≤ 20 mg/day given for ≤ 2 weeks and discontinued at least 2 weeks earlier was allowed.

The study was approved by the institutional review board of the Montpellier University Hospital, the coordinating centre for this nationwide study. Before inclusion, all patients gave their written informed consent to study participation.

Study design

The baseline assessment included a standardised interview; a general physical examination; blood cell counts; kidney function tests; viral serological tests (parvovirus B19, hepatitis B and C viruses, HIV); immunological tests (ELISAs for IgM, IgG and IgA rheumatoid factors and tests for anticitrullinated peptide antibodies (ACPAs) and antinuclear antibodies (ANAs)), HLA DR phenotype determination; a cytokine profile (IL-1R α , IL-6, IL-10, MCP-1, IL-4, IL-17, IFN γ , TNF α , IL-16 and IL-2); urine tests; radiographs of the chest, pelvis, hands and feet in the posteroanterior view; and radiographs of the feet in the oblique view. Renal failure was arbitrarily defined as serum creatinine >110 μ mol/L. Activity of the inflammatory arthritis was assessed at baseline through the disease activity score on 28 joints (DAS28) and the Ritchie index of joint tenderness, validated in the assessment of RA. Each patient was routinely evaluated by an ESPOIR study rheumatologist every 6 months for 2 years and then once a year for at least 10 years.

Antibodies against *Borrelia* were sought routinely in 2006, using IgG and IgM ELISAs (EuroImmun, BioAdvance, Philadelphia, Pennsylvania, USA) on blood samples collected, stored (-80°C) and centralised at inclusion into the cohort. Western blot confirmation was not obtained routinely as part of this project. All serological tests were conducted at the microbiology unit of the Brest university hospital, after the end of patient inclusion, independently from the physician's strategy for detecting a possible spirochetal infection at the first visit or during follow-up. Neither the investigators nor the patients were informed of the results of routine serological testing.

Diagnosis of Lyme arthritis

For each patient, we reviewed the most likely diagnosis at the first visit, the diagnosis recorded after 2 years of

follow-up, and all the information available after the last visit. We used these data to determine whether Lyme arthritis as the cause of the baseline disease presentation was confirmed, suspected or excluded. Thus, there was no standardisation of the procedure to confirm the diagnosis of Lyme arthritis. The decision to perform ELISA, Western blot and/or PCR tests to confirm the diagnosis of Lyme arthritis was up to the rheumatologist in charge of the patient.

Statistical analysis

We first recorded the prevalence of Lyme antibodies at baseline in the overall population and in subgroups defined by geographic area of residence. We considered that a diagnosis of Lyme arthritis could not be excluded on the basis of serology in patients with IgG positivity. Isolated IgM positivity was not considered as suggestive of Lyme arthritis according to articular symptoms duration. We determined the proportion of patients with a final diagnosis of Lyme arthritis and the diagnostic accuracy of Lyme serology in patients with recent-onset arthritis. Potential associations linking baseline clinical and biological characteristics to Lyme serology results were assessed using SPSS V.21.0 software (SPSS Inc, Chicago, Illinois, USA). We used the χ^2 test or Fisher's exact test, as appropriate, or the Mann-Whitney test. According to Bonferroni's correction for multiple comparisons, only p values ≤ 0.002 were considered statistically significant.

RESULTS

Lyme serology results in the overall cohort and in each geographic area

Among the 814 patients included in the ESPOIR cohort, 810 (99.5%) were tested for *Borrelia* antibodies. Among them, 657 (81.1%) were negative for IgM and IgG antibodies, 91 (11.2%) had only IgM antibodies, 49 (6%) had only IgG antibodies, and 13 (1.6%) had IgM and IgG antibodies. Thus, 62 (7.6%) patients had results that did not exclude the possibility of Lyme arthritis (IgG with or without IgM antibodies) (table 1).

The prevalence of IgG antibodies varied significantly by geographic area of residence (from 2.4% to 14.9%)

(figure 1). Prevalence was highest in Alsace (14.9%), the region of highest endemicity in France. A high prevalence of 12% was also found in the Ile-de-France region. Four of the 10 regions had prevalences lower than 5% (Bretagne, 3.8%; Centre, 2.9%; Midi-Pyrénées, 2.6%; and Languedoc-Roussillon, 2.4%). IgG antibodies were significantly more prevalent in the northern and north-eastern parts of France than in the other regions ($\chi^2=14.6$, $p<0.001$).

Diagnostic accuracy of Lyme serology in patients with recent-onset arthritis

Lyme arthritis was initially suspected in two patients but was confirmed in neither. Moreover, the prospective follow-up has secured an alternative diagnosis in both patients. Thus, in the cohort of 810 patients, routine Lyme serology incorrectly suggested the possibility of Lyme arthritis in 7.6% of patients. Table 2 details the final diagnoses in the patients with positive Lyme serology results.

Factors influencing Lyme serology results

The final diagnosis given after 2 years of follow-up was not significantly different between patients with and without positive Lyme serological tests. Body weight was significantly lower in IgM-positive than in IgM-negative patients (65.0 vs 68.7 kg, $p=0.02$). IgG positivity was significantly associated with higher values of the mean Ritchie index for joint tenderness (24.3 vs 17.1, $p=0.002$) and non-significantly associated with higher values of the mean DAS28 (5.4 vs 5.1, $p=0.05$) (table 3).

The proportion of patients with lymphopenia was higher among the patients with IgM and IgG antibodies than among the other patients (3/13 vs 47/796, $p=0.04$). The mean erythrocyte sedimentation rate was higher in IgM-positive than in IgM-negative patients (33.8 vs 28.8 mm/h, $p=0.05$), whereas no differences were found across subgroups for C reactive protein levels. The proportion of patients with renal failure was higher in patients who had IgG antibodies with or without IgM antibodies compared with the other patients (5/60 vs 12/738, $p=0.006$; and 2/13 vs 15/785,

Table 1 Lyme serology results according to the region of inclusion

Region	IgM-/IgG-	IgM+/IgG-	IgM-/IgG+	IgM+/IgG+	Total
Alsace	59 (79.7%)	4 (5.4%)	9 (12.2%)	2 (2.7%)	74
Aquitaine	30 (85.7%)	3 (8.6%)	2 (5.7%)	0 (0%)	35
Bretagne	38 (71.7%)	13 (24.5%)	2 (3.8%)	0 (0%)	53
Centre	64 (92.7%)	3 (4.3%)	1 (1.4%)	1 (1.4%)	69
Haute-Normandie	66 (84.6%)	7 (9%)	5 (6.4%)	0 (0%)	78
Ile-de-France	193 (77.2%)	27 (10.8%)	24 (9.6%)	6 (2.4%)	250
Languedoc-Roussillon	64 (79%)	15 (18.5%)	1 (1.2%)	1 (1.2%)	81
Midi-Pyrénées	64 (83.1%)	11 (14.3%)	0 (0%)	2 (2.6%)	77
Nord-Pas-de-Calais	44 (81.5%)	6 (11.1%)	4 (7.4%)	0 (0%)	54
Picardie	35 (89.7%)	2 (5.1%)	1 (2.6%)	1 (2.6%)	39
Overall	657 (81.1%)	91 (11.2%)	49 (6%)	13 (1.6%)	810

Figure 1 Prevalence of IgG antibodies according to the region of inclusion (map produced by DrawMeAGraph.com). The white areas correspond to regions with no data. The green areas correspond to regions with available data, the colour intensity being proportional to the prevalence of IgG antibodies.

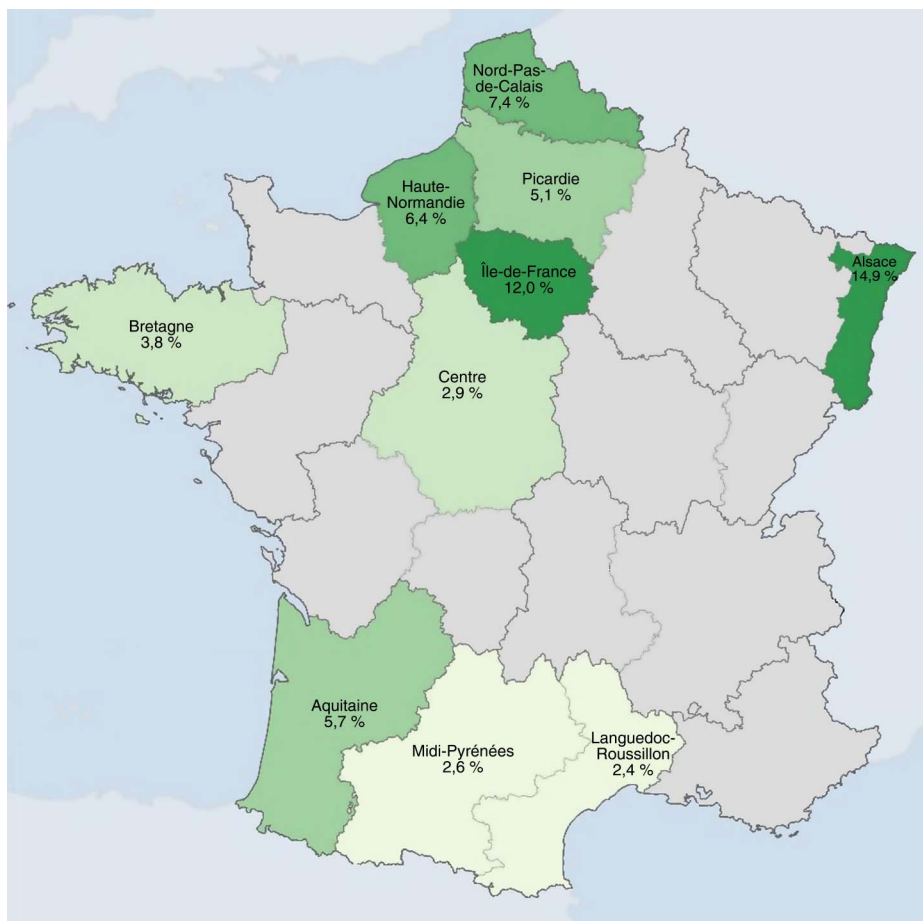


Table 2 Final diagnoses of patients with positive Lyme serology

Serological results	Final diagnoses
IgM+/IgG+ (13 patients)	9 Rheumatoid arthritis 2 Unclassified arthritis (Including 1 transient inflammatory arthritis that recovered after NSAID use and 1 chronic inflammatory arthritis controlled by methotrexate) 1 Sjögren's syndrome 1 Viral arthritis
IgM-/IgG+ (49 patients)	37 Rheumatoid arthritis 7 Spondyloarthritis 3 Unclassified arthritis (Including 2 undifferentiated arthritis controlled by DMARDs+NSAID and 1 transient inflammatory arthritis with immune profile evocative of RA) 2 Sjögren's syndrome
IgM+/IgG- (91 patients)	68 Rheumatoid arthritis 12 Unclassified arthritis 4 Spondyloarthritis 2 Osteoarthritis 1 Viral arthritis 1 Systemic lupus erythematosus 1 Complex regional pain syndrome 1 Sjögren's syndrome 1 Hepatitis C virus-related cryoglobulinaemic vasculitis

DMARDs, disease-modifying antirheumatic drugs; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis.

Table 3 Clinical and biological parameters according to Lyme serology results

Features	IgM+	IgM–	p Value	IgG+	IgG–	p Value	IgM+ and/or IgG+	Not IgM+ and/or IgG+	p Value	IgM+ and IgG+	Not IgM+ and IgG+	p Value
Females, n/N (%)	85/104 (81.7)	536/706	0.21	43/62 (69.3)	578/748	0.16	118/153 (77.1)	503/657 (76.6)	0.92	10/13 (76.9)	611/797 (76.7)	1*
Weight (kg), mean (SD)	65 (11.7)	68.7 (14.1)	0.02	68.5 (14.3)	68.2 (13.8)	0.88	66.5 (13.0)	68.6 (14.0)	0.09	64.1 (10.1)	68.3 (13.9)	0.50
Ritchie's index, mean (SD)	17.9 (17.7)	17.6 (17.2)	0.56	24.3 (21.1)	17.1 (17.1)	0.002	19.9 (20.0)	17.1 (16.8)	0.19	24.5 (25.5)	17.5 (17.3)	0.29
DAS28, mean (SD)	5.2 (1.3)	5.1 (1.3)	0.78	5.4 (1.4)	5.1 (1.3)	0.05	5.2 (1.4)	5.1 (1.3)	0.26	5.5 (1.0)	5.1 (1.3)	0.15
Lymphopenia <1000/mm ³ , n (%)	9/104 (8.6)	41/705 (5.8)	0.26	7/62 (11.3)	43/747 (5.8)	0.09*	13/153 (85.0)	37/656 (5.6)	0.19	3/13 (23.1)	47/796 (5.9)	0.04*
Neutrophils >7000/mm ³ , n (%)	88/103 (85.4)	606/697 (86.9)	0.67	52/62 (83.9)	642/738 (87.0)	0.44	128/152 (84.2)	566/648 (87.3)	0.30	12/13 (92.3)	682/787 (86.7)	1*
ESR, mean (SD)	33.8 (26.6)	28.8 (24.3)	0.05	30.9 (26.0)	29.3 (24.5)	0.86	32.7 (26.2)	28.7 (24.2)	0.09	32.9 (28.6)	29.4 (24.6)	0.74
CRP (IU/L), mean (SD)	19.1 (32.0)	20.4 (32.5)	0.30	22.8 (37.0)	20.0 (32.0)	0.30	20.2 (34.1)	20.3 (32.0)	0.44	23.3 (32.4)	20.2 (32.4)	0.84
Serum creatinine >110 µmol/L, n/N (%)	3/104 (2.9)	14/694 (2.0)	0.48*	5/60 (8.3)	12/738 (1.6)	0.006*	6/151 (4.0)	11/647 (1.7)	0.11*	2/13 (15.4)	15/785 (1.9)	0.03*
RF (IU/L), mean (SD)	94.1 (205.4)	123.6 (583.8)	0.01	117.3 (273.2)	120.0 (567)	0.84	106.7 (240.11)	122.9 (599.7)	0.02	57.3 (101.7)	120.8 (554.3)	0.65
ACPA (IU/L), mean (SD)	428.9 (1096.0)	486.6 (1491.8)	0.98	389.7 (935.4)	486.6 (1481.2)	0.37	440.5 (1072.8)	488.2 (1521.0)	0.88	104.9 (267.9)	485.3 (1457.2)	0.17

*By Fisher's exact test.

ACPA, anticitrullinated protein antibody; CRP, C reactive protein; DAS28, disease activity score on 28 joints; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

$p=0.03$, respectively). Mean rheumatoid factor titres were lower in the IgM-positive subgroup than in the other patients (94.1 vs 123.6 IU/L, $p=0.01$) (table 3). None of these differences was significant after Bonferroni's correction.

DISCUSSION

Routine Lyme serology was not useful for detecting cases of Lyme arthritis in French patients with recent-onset arthritis affecting more than one joint, as defined in the ESPOIR cohort. Thus, although 7.6% of patients had results that did not exclude the possibility of Lyme arthritis, no patients were given a definite diagnosis of Lyme arthritis. Among the clinical or laboratory features studied, only the Ritchie index was significantly associated with Lyme serology results after Bonferroni's correction. The prevalence of *Borrelia* antibodies varied widely across geographic regions of France.

Another study used less restrictive criteria than ours to include 90 patients who had arthritis onset within the last year and lived in non-endemic areas of France.¹⁰ None of the patients had positive Lyme serology results or a definite diagnosis of Lyme arthritis. A 2013 abstract reported a 4.5% seroprevalence of Lyme antibodies among 1180 patients who presented to the Leiden Early Arthritis Clinic in the Netherlands, including 8 (0.7%) given a definite diagnosis of Lyme arthritis.¹¹ The estimated positive predictive value was 10–28% overall but increased to 67% when the analysis was confined to patients with monoarthritis or oligoarthritis chiefly involving the large joints. Together with our results, these results do not support routine Lyme serology in patients with recent-onset arthritis affecting more than one joint and lasting for several weeks. Instead, the clinical features should be taken into account to determine whether Lyme serology is in order at the individual level. The apparently better performance of Lyme serology in the Leiden cohort should be interpreted in the light of the difference in Lyme disease prevalence between France and the Netherlands. Lyme disease is endemic in the Netherlands, where the estimated annual incidence is 133/100 000 population.^{12 13} In addition, the restrictive criteria used to select the ESPOIR cohort patients excluded patients with monoarthritis at the first visit and therefore probably led to the exclusion of typical Lyme arthritis cases. Overall, French patients with inflammatory arthritis affecting more than one joint and lasting for more than 6 weeks are not likely to have authentic Lyme arthritis.

That 7.6% of patients had positive serological tests yet none had definite Lyme arthritis deserves discussion. This global prevalence is within the limits of that usually found in French patients benefitting from Lyme serology (6–8.5%). However, in these selected populations, individuals are more likely to have authentic Lyme disease. The prevalence of IgG antibodies was highest (14.9%) in Alsace, the area of greatest endemicity in

France,³ and was higher in northern and north-eastern France than in other areas, in keeping with the previously described East-West and North-South gradients in the incidence of Lyme disease.¹⁴ These results suggest that some patients had acquired IgG antibodies during previous contact with *Borrelia*. Thus, in areas where *Borrelia* is prevalent in the tick population, routine Lyme serology as an aetiological assessment tool for recent-onset arthritis may carry a high risk of misleading results. Its use could increase the prescription of unnecessary and costly confirmatory tests and possibly the number of erroneous diagnoses of Lyme arthritis, leading to unnecessary treatments with antibiotics. Another explanation to the high proportion of positive serological tests, particularly for IgM antibodies, in patients without Lyme arthritis, involves a role for the technical characteristics of the ELISAs used and for the clinical setting in which the tests were performed. Among healthy persons living in regions of low endemicity, Lyme serological tests have an estimated false-positive rate of 2–5%.^{15–17} The most common infectious reasons for positive Lyme serology in patients without definite Lyme disease are other spirochetal infections such as syphilis, spirochetal periodontal disease and relapsing fever.^{18 19} None of these infections were documented in any of the patients with positive Lyme serology in the ESPOIR cohort. Rheumatic diseases can also lead to false-positive Lyme tests, especially for IgM antibodies,^{15–17} a fact that probably explains the substantial number of IgM-positive patients in our cohort.

Patients with positive Lyme serology did not differ from the other patients regarding the final diagnosis. However, patients with positive Lyme serology had higher values of several parameters reflecting the clinical or biological activity of inflammatory arthritis, including the Ritchie joint tenderness index, DAS28, and erythrocyte sedimentation rate; in contrast, rheumatoid factor titres were lower. After Bonferroni's correction, the only significant difference was for the Ritchie index, which was significantly higher in IgG-positive patients. Conceivably, patients with recent-onset arthritis who have specific immune profiles may be more likely to develop non-specific antibodies responsible for cross-reactivity.²⁰ However, these results should be interpreted with caution due to the small number of patients constituting the groups defined by the positivity of Lyme serology.

Our study has several limitations. First of all, the diagnosis of Lyme arthritis was not standardised and no confirmatory Western blots were routinely performed in patients with positive ELISAs. Although unlikely, the possibility of undiagnosed Lyme arthritis cases within the ESPOIR cohort remains questionable. Also, individuals with monoarthritis were not included in the ESPOIR cohort, while it is the most common initial manifestation of Lyme arthritis. As a result, our findings are limited to the specific cases of recent-onset arthritis affecting two or more joints.

CONCLUSION

This study does not support routine Lyme serological testing in patients with recent-onset inflammatory arthritis affecting more than one joint. Previous contact with *Borrelia burgdorferi* and background false-positivity due to the immunological setting may cause difficulties in interpreting the results of Lyme serological tests. When seeking to determine the cause of recent-onset oligoarthritis or polyarthritis, the appropriateness of Lyme serological testing should be determined on the basis of the history of a tick bite and/or EM and on the distribution of the arthritis.

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Competing interests None declared.

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Data sharing statement Studies conducted on the ESPOIR cohort are available on <http://www.lacohorteespoir.fr>

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