Holistic approach in patients with presumed Lyme borreliosis leads to less than 10% of confirmation and more than 80% of antibiotics failure.

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Summary:

In about 300 patients consulting for a presumed Lyme Borreliosis, this diagnosis was confirmed in less than 10% of patients whereas 80% were found with another disease. Overall the presumptive treatment administered before or after referral failed in about 80%.

Abstract:

Background: There is no precise idea whether patients with chronic symptoms attributed to Lyme borreliosis (LB) have LB or another disease.

Methods: We evaluated patients consulting for a presumed LB with a holistic approach including presumptive treatment. We included symptomatic patients who consulted with a presumed LB. They were classified as confirmed LB when they had four criteria, and possible LB if three with a positive clinical response to presumptive treatment.

Results: Amongst the 301 patients, 275 (91%) were exposed to tick bites, and 165 (54%) were bitten by a tick. At presentation, 151 patients (50.1%) had already been treated with a median of one (1-22) course of antimicrobials, during 34 (28-730) days. The median number of symptoms was three (1-12) with a median duration of 16 (1 – 68) months. Median number of signs was zero (0 – 2). ELISA was positive in 84/295 (28.4%) for IgM and 86/295 (29.1%) for IgG, and immunoblot was positive in 21/191 (10.9%) for IgM and 50/191 (26.1 %) for IgG. Presumptive treatment after presentation failed in 46/88 patients (52%). Diagnosis of LB was confirmed in 29 patients (9.6%), and possible in 9 (2.9%). Of the 243 patients with non-LB diagnosis, diseases were psychological, musculoskeletal, neurological or other origin in 76 (31.2%), 48 (19.7%), 37 (15.2%) and 82 (33.7%) patients respectively. Patients with other diseases were significantly younger, having more symptoms, a longest duration of symptoms, less clinical signs and less frequent LB positive serologies.

Conclusion: Overdiagnosis and overtreatment of LB is worsening, and health authorities should investigate this phenomenon.

Key words: Lyme borreliosis, differential diagnosis, presumptive treatment, holistic approach

Introduction

The National guidelines (NG) about Lyme borreliosis (LB) have been subject for much debate in many countries. The large consensus about the management of early manifestations of LB contrasts with the controversies around the approach of patients with chronic symptoms attributed to LB. The development of NG relies on evidence-based studies which are lacking for the approach of patient with chronic fatigue and other persistent symptoms attributed to possible or probable LB (1–3). Some physicians argue against these recommendations that amplify these controversies. As a result, suffering patients become lost between different approaches (4,5).

There are large numbers of patients with unexplained prolonged symptoms such as fatigue, impaired memory or concentration, headaches, arthralgia, myalgia, in whom persistent or chronic LB is suspected by some physicians without solid evaluation. It results in inappropriate overuse of health services, avoidable treatment-related illness, and substantial disability and distress (6,7). Such patients seek different medical advices, undergo many exams and receive several treatments. Therefore misdiagnosis and mistreatment of LB is associated with a social and financial cost (5). Recently, the mean cost of Lyme-related persisting symptoms has been estimated in the Netherlands around 5700 euros for an individual case (8). Not to mention, that long term usage of antimicrobials can cause alterations in the gut microbiote and can have impact on the immunity (9–11). However the importance of the misdiagnosis/mistreatment of LB phenomenon has not been extensively addressed during the last two decades.

These patients whether they have chronic symptoms associated to LB, or signs unrelated to LB cannot be left without a reasonable assessment (12). The needs for the most appropriate clinical management highlight the importance of a solid etiological diagnosis in patients consulting for presumably LB related chronic symptoms (13). On another hand and similarly to what has been observed in the chronic fatigue syndrome, such patients are often perceived by physicians as being over demanding and time consuming (14). A holistic approach is susceptible to overcome these limitations. It has been used in other fields of medicine (15). Applied to LB, it can be defined as patient-centered approach taking into account all the patient complaints and including a presumptive treatment when there is no obvious other diagnosis.

We evaluated patients consulting for a presumed LB with a holistic approach in order to find the etiology, and rule out or confirm LB suspicion. Patients with confirmed LB were compared with those diagnosed with a different disease to find factors associated with LB in this setting.

Methods

We included all the symptomatic patients who consulted a referral physician with a presumed diagnosis of LB from January 1st 2014 to December 31st 2017 at the infectious Diseases department at a University Hospital in Paris, France. Patients were screened through the database of the department's secretariat, and crossed with the own diagnostic list of the referral physician. The diagnosis of LB was presumed either by the patient himself, his general practitioner, or a specialist. The only criterion of inclusion was consulting for a presumed LB with symptoms lasting for at least four weeks. The criteria of exclusion were lost medical charts, absence of any symptoms or signs, absence of serological tests for LB except in case of ongoing erythema migrans (EM), and no possible estimation regarding the result of presumptive treatment. Authorization by the French National Commission for Data Processing and Liberties was obtained. No consent form was collected because our study is descriptive and retrospective.

Holistic approach was defined by a comprehensive approach of the patient, evaluating the history of presumed LB symptoms, his personal medical history, the past antimicrobial treatments, all symptoms and signs, the results of laboratory tests (including that of serologic tests for LB) and any other exams (X-Ray, MRI, CT scan) carried by the patient. It included a four-weeks course of antibiotic presumptively efficient in LB unless there was evidence of another diagnosis or failure of a previous well-conducted treatment. All the patients were followed up until a firm diagnosis was established, or referred to an internal medicine specialist in case of no established diagnosis.

The following variables were evaluated: age, sex, LB-related history (tick exposure, tick bites, erythema migrans), personal history, signs and symptoms (duration, number, neurological, rheumatic, cutaneous and other systems involvement), previous antimicrobial treatment (number of antimicrobials, duration of treatment), results of LB serology assays such as ELISA (enzyme-linked immunosorbent assay), and immunoblot, as well as other paramedical exams performed according to the signs and symptoms. Symptoms were grouped according to the organ system involvement (termed "symptomatic organs") because many patients have multiple symptoms complaints.

All past antimicrobial treatments were evaluated. Doxycycline (200 mg per day), ceftriaxone (2 gr per day), cefuroxime (500 mg per day) amoxicillin (50 mg/kg/day) were considered as efficient against LB depending on the clinical form according to guidelines (1-3). Therefore patients consulting for persistent symptoms despite at least four weeks of one of these treatments were considered as failure, and investigated for other diseases. Patients who did not undertake efficient antibiotic treatment and with suspicion of LB or no obvious other diagnosis were presumably treated for LB with either amoxicillin (50 mg/kg/d) in case of EM, ceftriaxone (2 gr per day) in case of neurological involvement or doxycycline (200 mg per day) in other instances and in case of beta-lactams intolerance for at least 28 days (except in case of EM where the duration was 15 days).

The patients were classified as confirmed LB when they met four criteria: tick exposure or bite, clinical signs characteristics of LB, positive IgM or IgG serological tests (ELISA and Western blot), and recovery after antibiotic treatment. Patients were classified as possible LB when they met three of these criteria including recovery after presumptive treatment. EM was classified as confirmed LB without taking into account the results of serological tests when available. Clinical signs were considered as characteristic of LB when they were mentioned in review articles or NG (1–3). The European classification was used (2). Unexplained prolonged symptoms such as fatigue, impaired memory or concentration, headaches, arthralgia, myalgia were not considered as characteristic of LB. Regarding immunoassays, the available ELISA and Western Blot, either IgM or IgG, were considered positive when they were above the cut off for the former and showing at least three positive bands for the later. Double step approach was considered except in patients with only ELISA or Immunoblot available at presentation. Patients were followed until recovery or referral. Recovery was defined as the disappearance of all signs and symptoms within three months after adequate treatment. Failure was defined as persistent of signs and symptoms after adequate treatment.

Patients without confirmed or possible LB were screened for other diagnosis according to their personal medical history, symptoms and signs at presentation, and the results of biological, serological, and radiological exams prescribed by the IDS (infectious diseases specialists) or the treating physician. Unless a diagnosis was reached after the first consultation, all the patients were seen at least one more time after being prescribed a presumptive antibiotic treatment to evaluate the results of the therapeutic challenge, and alternatively discuss the diagnosis options. Patients diagnosed with a disease other than LB were referred to the appropriate specialists (neurologist, rheumatologist, internal medicine, Ear, Nose and throat specialist) or psychologist (when the consulting physician found it necessary). The Diagnostic and Statistical Manual of Mental Disorders V were used to identify these disorders (16).

The patient's characteristics were recorded as counts or percentages for categorical variables, and medians and ranges for continuous variables. Analyses were done with Microsoft Excel 2010 and Epi Info 7 Software. Categorical variables were compared between patients with LB and those with other diseases by using the Fisher's exact test. Continuous variables were compared using Wilcoxon – Mann Whitney's test. Differences between groups were considered significant if $p\text{-}value \leq 0.05$.

Results

Of the 333 screened patients, 32 were excluded (Figure 1). The patients characteristics are summarized in table I. The diagnosis of LB was confirmed in 29 of the 301 patients (9.6%), and possible in 9 patients (2.9%). Of the 29 patients with confirmed LB, 10 had EM, 8 had neuroborreliosis, 7 had arthritis, and 4 had other cutaneous borreliosis. (Table II).

For statistical analysis we compared the 29 patients with confirmed LB and the 243 with another firm diagnosis. We thus excluded the 9 patients with possible LB and the 20 with no firm diagnosis from the analysis. The patients with a disease other than LB were significantly younger and more commonly found with more than one symptom, a longest duration of symptoms, less clinical signs and less frequently Lyme positive serologies (Table III).

Discussion

In about 300 patients consulting with a presumed LB, this diagnosis was confirmed in less than 10% of the patients whereas 80% were found with another disease. Overall the presumptive treatment administered before or after referral failed in more than 80%.

In this cohort of patients consulting with presumed LB we identified factors associated with diseases other than LB. The misbalance between the higher number of symptoms and the smaller number of signs was presumptive for a diagnosis other than LB. Factors were being younger, having a greater number of symptoms (median of three symptomatic organs per patient), less clinical signs (median of zero per patient), and less positive serologies (Table III). To the best of our knowledge such factors have not been highlighted before.

The finding that 80% of our patients were diagnosed with another disease is striking. LB over diagnosis seems to have amplified over the last twenty years when compared to similarly designed studies that were performed in the United States of America more than twenty years ago. During the late eighties, 57% of the 788 patients referred with presumed LB to a LB clinic in Boston, Massachusetts, were diagnosed with other diseases (6). In 1994/1995 amongst 209 US patients similarly referred to a LB clinic in Connecticut, 60% had no evidence of current or past LB whereas 21% met criteria for LB compared to 9% in our study (7). In North-eastern France where the incidence was estimated above 350/100.000 in 2016, the rate of over diagnosis seemed to be even higher, with serological tests coming back positive in 8% of 128 patients consulting for suspected LB and LB being the IDS' final diagnosis for only 3.6% of patients which is in line with our results (17,18).

Overtreatment for presumed LB has not worsened in similar proportion to over diagnosis. At presentation, 44.8 % of our 301 patients had already received the recommended duration of the adequate antibiotic course for a presumed LB. Similarly 51% of the 788 patients referred in Boston had received recommended treatment courses before referral (6). In contrast more than 75% of 209 patients with presumed LB in Connecticut had been treated before referral (7). However the median duration of antibiotic treatment at presentation was not so different, i.e. 75 days in the 40 patients with history of LB, and 42 days in the 125 patients with no evidence of past or present LB, respectively (7). In our study the median duration of antibiotic treatment was 34 days in our 151 treated patients at presentation. Overtreatment of LB delays the diagnosis of the alternate disease, its appropriate treatment, and thus impacts the quality of life.

However our patients have also received antimicrobial treatments other than the recommended adequate antibiotics against LB. The reason why patients may be over treated as such is beyond the scope of this research. However this has been comprehensively discussed 20 years ago. Surprisingly the ten reasons highlighted by the author to explain this phenomenon seem to be more or less the same today (5). We can even add some other limitations to overtreatment decision. It is not supported by the results of randomized trials evaluating prolonged duration of treatments in presumed LB (19–21). Moreover, it has been showed that short-term provision of antibiotics should be preferred in the treatment of LB (9). Therefore our role was more often to stop useless antibiotic treatment rather than prescribe or prolong them.

The leading etiology being found in 28 % of the 243 cases with diseases other than LB was psychological disorders. The spectrum of psychological disorders is large and includes post-traumatic stress disorders (PTSD), burnout syndrome, moral or sexual harassment, and depression (table II). Higher rates of depression (38% and 42%) and stress (52% and 45%) have been found in the 1990s in 40 patients with history of LB, and 125 with no evidence of LB, respectively (7). Depression and stress have already being underlined as a cause of alternate diagnosis, being diagnosed in 29.3% of 437 patients with no clinical LB and negative serology from the Netherlands but without any significant difference between the group of patients diagnosed with LB and the comparative group with no LB (22). Confusion between some of these psychological disorders cannot be ruled out as they share the same pattern of somatoform signs with neurocognitive disorders, different kind of chronic pains and fatigue (23). Moreover moral or sexual harassment could cause depression, PTSD or burnout syndrome. However it shows that physicians facing such patients should have in mind all these disorders, evaluate them this way, and thus refer them to specialists.

Our study also shows the large spectrum of diseases found in these patients including multiple neurological diseases (multiple sclerosis, Charcot disease, neurogenetic disorders…), rheumatologic or musculoskeletal diseases (scoliosis, arthritis, arthrosis…), some ID, and sleep apnea syndrome. This is not surprising given that all these diseases can be misleading with clinical forms of LB (2). These were also within the range of diseases diagnosed in American patients in the nineties (5,6). This shows that physicians may still treat LB whereas there is other and sometimes obvious alternate diagnosis. On another hand the treating physicians missed the diagnosis of LB in a dozen of our 29 confirmed cases of LB, the other half of the patients with active LB being referred by their general practitioner or specialist. Such patients are facing a double challenge, being over treated by some physicians but also being neglected by others.

Twenty of our patients with complaints not related to LB remained without any firm diagnosis other than somatoform symptoms of unknown origin. Despite the absence of characteristic signs we cannot rule out the possibility of infection by another tick-borne microbial agent such as *Anaplasma phagocytophilum*, *Candidatus Neoehrlichia mikurensis*,

Rickettsia helvetica, *Rickettsia monacensis*, *Borrelia miyamotoi* and several *Babesia* species as showed during co-infections with LB (24). Ticks can carry such microbial agents whose deoxyribonucleic acid can even been found in blood of patients exposed to tick bites. However this possibility cannot be overstressed. Based on molecular detection techniques, the probability of infection with such tick-borne pathogens after a tick bite has been estimated roughly about 2.4% in patients from the Netherlands with history of EM (25). Moreover and similarly to our patients none of these positive individuals reported any overt symptoms that would indicate a corresponding illness during the three-month follow-up period (25). In the northeastern regions of France, among asymptomatic forestry workers, the seroprevalence estimated for these pathogens was 5.7% for *Francisella tularensis*, 2.3% for tick-borne encephalitis virus, 1.7% for *Anaplasma phagocytophilum*, 1.7% for *Bartonella henselae*, 0.1% for *Babesia divergens* and 2.5% for *Babesia microti* while seroprevalence for LB was 14.1% (26). Moreover such patients were treated with doxycycline that was not efficient although covering some of these microbial agents.

In our study the diagnosis relied on four criteria including recovery after presumptive treatment as we considered such practice associated with our holistic approach. Indeed the serological diagnosis of LB has some limitations as evidenced in our subset of patients with early LB (false negative) and other diseases (false positive mainly IgM). This was not the main purpose of our study to focus on LB serologies. It is well known that the performance of serological assays varies according to commercially available ELISAs and immunoblots with divergent sensitivity and must be interpreted with caution taking into account the epidemiological and clinical signs (27,28). We were not able to perform the biological assays in the French referral center, and we took into account different assays, but always including an ELISA and/or an immunoblot marketed in France. Recovery after antibiotics was considered as the fourth pillar of LB diagnosis making the diagnosis confirmed or possible. This guarantees that the diagnosis of LB was as accurate as possible but we cannot rule out the possibility of other doxycycline susceptible disease or placebo effect in our patients with possible LB.

Our study has some limitations. It is a monocentric study and is based on the experience of a single referral physician, as this holistic approach is very particular needing some background knowledge or interest in psychology. Of note, most of the IDS working in our department find these patients as being over demanding as showed in another French study where the modal duration of consultation for suspected LB was estimated at 30-60 minutes (which is line with our experience although not evaluated more precisely here)(18). Moreover the IDS consider that most of these patients have no ID, which is confirmed in our study with only ten ID diagnosis other than LB, and has been underlined previously (5–7). Another limitation is related to the serologic tests that were not performed at the National reference center, and therefore may have different sensitivity and specificity (27,28). However the tests available in France are validated before marketing. Therefore the

diagnosis procedure took into account the results of the presumptive treatment that makes the diagnosis of LB more stringent.

Conclusion:

In conclusion over diagnosis and over treatment of LB is a real cause of concern, and a worsening phenomenon. Too many patients were treated with useless antibiotics for longer duration. This carries a risk for the patient and the community. The reasons why this phenomenon is amplifying despite growing reasons not supporting such a deleterious trend, needs to be investigated.

Author contribution:

EC designed the study. KC, SJ, GM and VP contributed to the collection of data. EH and KC did the data analyses. EH and EC wrote the first draft of the manuscript.

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Table 1: patients' characteristics

Variables (n=)	Number of patients*	Percentage %	Median (Min-Max)
Sex (n=301)			
Male	183	60.8%	
Female	118	39.2%	
Age (years)	301		50 (12-85)
Place of living (n=296)			
Ile de France	228	75.7%	
Outside Ile de France	68	22.6%	
Tick exposure (n=300)	275	91.4%	
Tick bites (n=301)	165	54.8%	
History of erythema migrans (n=300)	44	14.6%	
Median number of symptomatic organs			3 (1-12)
Median duration of illness			16 (1-68) months
Median number of clinical signs			0 (0-2)
No clinical sign (n=301)	181	59.0%	
One clinical sign (n=301)	102	33.0%	
Neurological sign (n=102)	35	34.3%	
Rheumatic sign (n=102)	24	23.5%	
Cutaneous Manifestation (n=102)	25	24.5%	
Ophthalmological signs (n=102)	5	0.1%	
Other involvements (n=102)	13	12.7%	
Two clinical signs (n=301)	18	6.0%	
ELISA IgM (n=295)	84	28.4%	
ELISA IgG (n=295)	86	2910.0%	
WB IgM (n=191)	21	10.9%	
WB IgG (n=191)	50	26.1%	

n: number of patients in whom this variable was evaluated
*: number of patients found with the corresponding variable.

Table II: Final diagnosis in 301 patients consulting for a presumed Lyme borreliosis

Diagnostic	***Number of patients n= 301***	***Percentage% n=301***	***Affected systems***	***Number of patients***	***Percentage%***
Confirmed Lyme	29	9.6%	Erythema migrans	10	34.4
			Articular	7	24.1
			Neurological affections	8	27.5
			Cutaneous	4	13.8
Possible Lyme	9	3%			
Non-Lyme Diseases	243	80.7%			
Psychological disorders	76	25.2%	Depression	30	39.4
			PTSD[3]	26	34.2
			Burnout	15	19.7
			Harassment	3	3.9
			Other	2	2.6
Rheumatology	48	15.9%	Osteoarthritis	19	39.5
			Scoliosis	11	22.9
			Other	18	37.5
Neurological pathologies	37	12.3%	ALS[1]	3	8.1
			Parkinson	4	10.8
			Small fiber disease	3	8.1
			MS[2]	5	13.5
			Other	22	59.4
Sleep Apnea Syndrome	15	4.9%			
Association of pathologies	16	5.3%			
Various affections[4]	51	16.9%			
Undetermined affections	20	6.6%			

[1]ALS: amyotrophic lateral sclerosis
[2]MS: Multiple sclerosis
[3]PTSD: Post-traumatic stress disorder
[4]Various affections including thyroid (6), fibromyalgia (5), cardiomyopathy (3), infectious diseases (10), inflammatory diseases (3) and others (24)

Table III: Comparison between confirmed LB patients (n = 29) and the patients who have other confirmed diagnosis (n = 243).

Variables (range)	Confirmed Lyme		Non Lyme		Test	p-value
Sex (n= 272)	**Female**	14	**Female**	158	F[1]	0,10
	Male	15	**Male**	85		
Median of age (n=272)	55 (30-79)		50 (14-85)		W[2]	0,036
Ile de France (N=267)	21/29	72.4%	187/238	78.5%	F[1]	0,47
Median duration of illness, months (n=272)	4 (1 - 96)		20 (1 - 68)		W[2]	$2,19X10^{-7}$
Median duration of treatment, days	36 (28 – 60)		38 (28 – 395)			
Median number of treatment (n=272)	0 (0 -3)		1 (0 - 13)		W[2]	0,0001
Median number of symptoms (n=272)	1 (0 - 4)		3 (0 - 11)		W[2]	$4,78\ X10^{-9}$
Median number of clinical signs (n=272)	1 (0 - 2)		0 (0 - 2)		W[2]	$1,8 \times 10^{-7}$
Tick exposure (n=272)	29/29	100%	221/243	90%	F[1]	0,14
Tick bites (n=272)	**14/29**	48.3%	**131/243**	53.9%	F[1]	0,55
Erythema migrans (n=261)	**5/19**	26.3%	**31/242**	12.8%	F[1]	0,15
ELISA IgM (n=261)	**14/25**	56%	**61/236**	25.8%	F[1]	0,004
ELISA IgG (n=265)	**20/25**	80%	**56/240**	23.3%	F[1]	$2,85x\ 10^{-8}$
WB IgM (n=132)	**7/12**	58.3%	**13/120**	10.8%	F[1]	0,0003
WB IgG (n=133)	**16/16**	100%	**27/117**	23%	F[1]	$1,48x\ 10^{-9}$

[1]F: Fisher's exact test;
[2]W: Wilcoxon - Mann Whitney's test

Figure 1.

Figure 1: Flow chart from the inclusion of 333 patients till the final diagnosis of Lyme borreliosis or other diseases