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**Focus on patients receiving long-term antimicrobial treatments for Lyme borreliosis:
no Lyme but mostly psychiatric disorders**

O. Itani, E. Haddad, V. Pitron, F. Pichon, E. Caumes

INTRODUCTION

Overdiagnosis and overtreatment of Lyme borreliosis is frequent [1]. Recent studies have found that only 10 to 15% of patients consulting with a presumed diagnosis of Lyme borreliosis were actually found with Lyme borreliosis [2-5]. Psychiatric disorders, including somatic symptom and related disorders as well as depressive disorders, were found in 25% of 301 patients in Paris, France [2], and 42.5 % of 209 patients in Connecticut, USA [6].

Overdiagnosing Lyme borreliosis leads to overtreatment. In two recently published studies, the rates of overtreatment were respectively 60% of 301 patients in Paris [2], and 84% of 911 patients in Baltimore, USA [5]. Moreover, the maximum duration of treatment was 395 days in the Paris study [2] and reached 2555 days in the Baltimore study [5].

By overtreating Lyme borreliosis, the underlying true disease remains undiagnosed and may progress. We evaluated patients referred with a presumptive diagnosis of Lyme borreliosis and receiving anti-microbial treatment for at least 180 days.

PATIENTS AND METHODS

We performed a retrospective observational monocentric study in the Infectious Diseases Department at the Pitié Salpêtrière University Hospital in Paris, France. We included all patients referred between January 1st, 2014 and June 30th, 2019 with a presumptive

diagnosis of Lyme borreliosis for which they received antimicrobial treatment for at least 180 days. The study being observational and retrospective, no consent form was collected.

Patients' charts were screened for a presumptive Lyme borreliosis diagnosis through the database of outpatients of a single physician crossed with his diagnostic list. Clinical and serological criteria for diagnosing Lyme borreliosis were based on The European Classification [7]. Patients receiving antimicrobial treatment for less than 180 days were excluded.

Data on patient demographic (age, sex), Lyme borreliosis-related history (tick exposure, tick bites, erythema migrans), symptoms (duration, type and number of symptomatic organs), results of Lyme borreliosis serology assays (Enzyme-linked immunosorbent assay and Immunoblot), antimicrobial treatment (type, number, duration), and analgesics (type, number) were evaluated. Duration of antimicrobial treatment was defined as the time from the initial start of treatment. Because these patients were commonly prescribed successive antimicrobial courses, we deleted treatment-free days and evaluated cumulative days of treatment.

Finally, adverse drug events and final diagnoses were evaluated. Adverse drug reactions were evaluated according to the French rules [8]. *The Diagnostic and Statistical Manual of Mental Disorders, V*, was used to identify psychiatric disorders [9].

Data were expressed as counts and percentages for categorical variables and as means for continuous variables. Analyses were done using Microsoft Excel 2011.

RESULTS

Of the 425 screened patients, 15 (3.5%) had received over 180 days of antimicrobial treatment: 11 (73%) were women, the median age was 44 (15–89) years, 7 (47%) were exposed to tick bites, and 4 (27%) were bitten by a tick. Median number of symptomatic organs was 4 (1–8) and median symptoms duration was 63 (6–240) months. Median duration of treatment was 476 (180–942) days. (Table)

Serologic testing by ELISA was performed in 14 patients: 10 had negative results and 4 had positive results that were not confirmed with Western Blot. One patient without serologic testing by ELISA had negative results with Western Blot only. (Table)

For one patient, the list of the antimicrobial treatments was not available. Among the remaining 14 patients, the most common antimicrobial treatments were macrolides (93%), anti-parasitic drugs (73%), tetracyclines (67%), and beta-lactam antibiotics (60%). Median number of antimicrobial treatment was 6.8 (1–18) per patient. Nine patients (60%) were also treated with analgesics with a median number of 1.4 (0–7) drugs per patient. (Table)

Adverse effects occurred in 4 patients (27%) with a median number of 0.6 (0–4) adverse effects per patient. They included antibiotic-associated colitis (*Clostridium difficile*) (1 case), fungal infections (oral thrush and genital candidiasis, 3 cases), and various adverse drug reactions (3 cases). (Table)

There were no cases of confirmed Lyme borreliosis, and all our patients had other definable illnesses as cause of their complaints. The final diagnosis was a psychiatric disorder in 9 patients (60%): somatic symptom and related disorders (5 cases), depressive disorder,

bipolar disorder, post-traumatic stress disorder, and factitious disorder imposed on another; a neurological disorder in 3 patients (20%): migraine with aura, Parkinson's disease, and cervical myelopathy; and various diseases for the three remaining patients: poly-pathologies, tuberculosis, and sleep apnoea syndrome. (Table)

DISCUSSION

Among these 15 patients, none had confirmed Lyme borreliosis, and 60% were diagnosed with a psychiatric disease. The mean antimicrobial treatment duration was 476 days, resulting in adverse effects among 27% of them.

In our population of 425 patients referred for presumptive Lyme disease, only 15 (3.5%) had received an antimicrobial treatment for more than 180 days. Previous studies reported greater numbers, with 14.5% of 165 patients treated more than 150 days in Connecticut [6], and 11% of 1061 patients treated more than 183 days in Baltimore [5]. Our finding is possibly under-estimated because patients were referred to a single physician whose stances against the chronic form of Lyme borreliosis are known.

Patients were predominantly women, which is consistent with results of previous studies. In Connecticut, 65% of patients without Lyme borreliosis were women [6], whereas the same figure of 65% was found in Paris [2] and in Baltimore [5]. Over-representation of women in these cohorts of patients without Lyme borreliosis is probably related to the differential diagnoses that include a large part of psychiatric disorders. Indeed, it has been shown that somatic symptom and related disorders, which are the leading cause of consultations in this setting, are more commonly found in women [10].

Unsurprisingly none of our patients had Lyme borreliosis which underlines the growing phenomenon of Lyme borreliosis overdiagnosis. This phenomenon is fostered by patients' associations, important media coverage and the Internet, which spread inaccurate information and contribute to creating public confusion and anxiety [11]. Moreover very few of our patients had Lyme borreliosis-related history as only 47% had been potentially exposed to ticks, 27% reported tick bites and none reported erythema migrans or had positive serological testing.

Overdiagnosing Lyme borreliosis leads to undiagnosed underlying diseases. Nine (60%) of our patients were diagnosed with psychiatric diseases including 5 cases of somatic symptom and related disorders. This finding reflects its increasing prevalence in the general population and in all medical settings, including non-psychiatric ones [12]. Indeed recently reported prevalence rates for somatic symptom and related disorders vary between 16.1% and 57.5% in primary care patients with a 12-month prevalence of 11% in the general population [12]. Diagnosis of somatoform disorders is complex and therefore often delayed. Physicians may fear missing an organic disease and thus refrain from recognising such disorders. Patients remain with long-term unexplained complaints leading them to repeatedly use health services, which can be a wearisome and frustrating experience for both physicians and patients [12]. Failure to diagnose psychiatric disorders may lead to worsening their substantial distress, or even increase suicidal behaviours. On the contrary, correctly labelling the disorder can help legitimize their complaints and start targeted treatment.

Our other final diagnoses included neurological disorders, tuberculosis, sleep apnoea syndrome, and poly-pathologies. Previous studies reported similar findings. In Connecticut 8% of 165 patients were assigned with a neurological disorder [6]. In Paris, among 301 patients, 12% had a neurological disorder, 5% had sleep apnoea syndrome and 5% poly-pathologies, although some of these patients were included in both studies [2]. Failure to diagnose the underlying disease leads to progression of severe and potentially contagious diseases, such as tuberculosis in one of our cases. With this in mind, it seems crucial to pursue etiological searches so as to provide appropriate care.

Antimicrobial treatments included drugs not known to be efficient against Lyme borreliosis, such as fluoroquinolones, trimethoprim/sulfamethoxazole, anti-parasitic drugs, antifungals and antivirals [7]. As highlighted by other authors, we believe that physicians, who claim to treat chronic forms of Lyme borreliosis, propose widespread treatments to cover all potential diagnoses [5]. Indeed their prescriptions include antimicrobial treatments intended to treat other tick-borne diseases. However, presumptive treatments also target potential side effects of antibiotics, which explains the prescription of metronidazole (for antibiotic-induced colitis) and fluconazole (for muco-cutaneous candidiasis). Moreover 60% of our patients were treated with different analgesics, sometimes up to opioids, which show that antimicrobials were not efficient in this subset of patients.

Adverse effects occurred in 4 patients (27%), which is much less than the rates of 55% of minor and 6% of major adverse effects found in one study [6]. Our finding is probably

under-estimated because data was collected retrospectively and adverse effects were not specifically investigated. Some of the adverse effects noted were severe (colitis, prolongation of QT interval, sight impairment). This supports the general attitude of avoiding long-term antimicrobial treatment.

Our study has some limitations. As a retrospective observational study, it was subject to missing data resulting in under-estimating certain variables (treatment detail, analgesics, adverse effects). The aforementioned referral bias was another limitation. Our population was possibly different from other settings because based on the experience of a single physician in a single-centre at an academic hospital. Finally, data was evaluated on a limited number of patients.

CONCLUSION

Patients receiving treatment for presumed Lyme borreliosis for more than six months need a comprehensive approach including psychiatric expertise.

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