Efficacy of a long-term antibiotic treatment in patients with a chronic Tick Associated Poly-organic Syndrome (TAPOS)

Efficacité d’une antibiothérapie au long cours pour un « syndrome poly-organique postmorsure de tiques » (SPOT) chronique

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Abstract

Settings. – Despite a now codified antibiotic treatment for Lyme disease, a significant proportion of patients treated according to recommendations complain of persistent signs and symptoms. The pathophysiological mechanisms which underlie this syndrome of post-treatment chronic systemic illness remain unclear. For some physicians post-treatment symptoms indicate a persistent infection requiring prolonged antibiotic therapy. For others, there is no benefit from antimicrobial therapy. The difficulty of assessment encountered in studies is significant because many symptoms are subjective. We think that the term “chronic Lyme disease” is not appropriate and should be replaced by chronic “tick associated poly-organic syndrome” (TAPOS).

Objective. – This open-label prospective study was made on a group of 100 patients having followed a medical treatment for a chronic TAPOS and to evaluate their evolution under prolonged antibiotic treatment.

Results. – The medical management was found to be effective for symptoms, especially for patients with a high probability of chronic TAPOS (NEJM score). Patients with post tick-bite symptoms, which often worsens their quality of life, deserve particular attention.

Conclusion. – This study had methodological limitations but could help in terms of feasibility, choice of inclusion criteria, and design of follow-up for a future randomized, double blind study to test for an optimal management of TAPOS.

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Résumé

Contexte. – Malgré un traitement antibiotique désormais consensuel de la maladie de Lyme, une part significative de patients correctement traités présentent des signes chroniques. Les mécanismes physiopathologiques impliqués dans ce « syndrome poly-organique postmorsure de tiques » demeurent mal connus. Pour certains cliniciens, ce syndrome est lié à la persistance d’une infection bactérienne et requiert une antibiothérapie prolongée. Pour d’autres, il n’y a pas de bénéfice à traiter par antibiotiques. L’évaluation de l’efficacité des traitements est rendue difficile du fait du caractère subjectif des symptômes. Nous pensons que le terme de Lyme chronique est inapproprié et proposons donc l’appellation de « syndrome poly-organique associé à une morsure de tiques » (SPOT).

Objectif. – L’objectif de cette étude prospective monocentrique est de décrire les symptômes du SPOT et l’évolution sous traitement antibiotique prolongé de 100 patients.

Résultats. – L’efficacité du traitement antibiotique prolongé semble plus nette chez les patients ayant une forte probabilité de SPOT (score NEJM). Les patients ayant des troubles chroniques subjectifs avec un fort impact sur la vie courante méritent une attention particulière.

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1. Introduction

Among tick-born infections, Lyme disease is universal and may cause acute, subacute or chronic signs and symptoms. Lyme disease is an initially cutaneous anthropozoonosis that may disseminate secondarily. This disease is caused by a bacterial pathogenic agent, Borrelia burgdorferi sensu lato, transmitted by an arthropod vector, the Ixodes tick [1]. The erythema migrans, which represents the early phase of the disease, was described at the beginning of the 20th century [2]. The secondary disseminating phase allowed to define the disease, following an epidemic of arthritis reported by Burgdorfer, at Lyme in 1982, in Connecticut [3]. When adequate antibiotic treatment is not prescribed in the early phase of the disease, the evolution may lead to chronicity. The diagnosis of chronic Lyme disease must be suggested, if there is a history of a remote tick-bite and/or an erythema migrans, and if the patient presents with symptoms involving various organs (central nervous system, joints, myocardium...) sometimes objective, often subjective associated with a positive B. burgdorferi serology or a prior antibody response. Even if the disease is now well documented, diagnostic and therapeutic issues remain. There is no formal test for the diagnosis, except for isolation of the pathogen in situ, which is a complex task [4]. Serology, currently the main diagnostic tool, must be interpreted cautiously, particularly in Europe because of important limitations regarding the test sensitivity and specificity [5–7]. Cases of seronegative Lyme disease proven by isolation of B. burgdorferi in patients have been reported [8–11]. In a recent prospective study conducted in patients presenting with a chronic symptomatology suggesting Lyme disease, 45% had a negative B. burgdorferi serology [12]. All these seronegative patients had a history of tick-bite and erythema migrans skin lesions. Even if the antibiotic treatment is now codified, a significant proportion of patients treated according to the recommendations complain of persistent signs and symptoms. This syndrome of post-treatment chronic Lyme disease (PTCLD) is a systemic illness persisting after adapted treatment, with severe fatigue, myalgia, polyarthralgia, paresthesia, and mood or memory disorders [13–15]. The pathophysiological mechanisms which underlie this syndrome, remain unclear. Several hypotheses have been discussed in the literature. The usual explanation is that it could be a post-infectious autoimmune syndrome or strictly sequels. It could also be due to the persistence of B. burgdorferi able to escape the immune response, or to co-infection by other pathogens [16–20]. These co-pathogens (other bacteria, or even parasites such as Babesia) could also be inoculated by ticks. There is no consensus on this chronic disease’s pathology [21]. For some physicians post-treatment symptoms indicate persistent infection requiring prolonged and intensive antibiotic therapy [22]. For others, there is no benefit from antimicrobial therapy [23–25].

A clear-cut answer to these questions cannot be currently given, due to the difficulty of evaluation encountered in the studies. Many symptoms are subjective, there are often no biological abnormalities, microbiological or serological criteria for diagnosis are often not reliable, and there are no microbiological criteria for cure. Since the etiology is not clear, we think that the term chronic Lyme disease is not appropriate and should be replaced by chronic “tick associated poly-organic syndrome” (TAPOS). The objective of this study was to prospectively describe a group of patients having sought medical treatment for a chronic TAPOS and to evaluate their evolution under long-term antibiotic treatment.

2. Patients and methods

In this open-label prospective study, we analyzed 100 patients having consulted in the Infectious Diseases Unit between January 1999 and July 2002, for chronic TAPOS and answering inclusion criteria. Inclusion criteria were 18 years of age or more, presenting with chronic symptomatology (greater than 6 months) compatible with what already had been described as chronic Lyme disease in NEJM [12] articles and with either a history of erythema migrans, positive B. burgdorferi serology, or tick-bite. The patients had to have been already treated with an antibiotic course recommended for the primary or the secondary phase of Lyme disease. They should not have previously received a prolonged antibiotic treatment (longer than four weeks), and should not have received antibiotics or anti-inflammatory drugs in the three previous months. Patients presenting with primary forms of Lyme disease with recent tick-bites, and secondary forms (acute meningoradiculitis, myocarditis, arthritis) were not included in the study. Patients had to agree to be followed for at least three months, and if possible six months. All data was collected prospectively, by means of a standardized questionnaire and medical observation. In addition to sex and age, clinical signs and symptoms were described at inclusion (day 0), at month 3 of antibiotic treatment, and when possible at month 6. Suggestive signs and symptoms were classified in nine organ categories (neurological, articular, systemic, psychiatric or cognitive, cutaneous, cardiorespiratory, muscular, gastro-intestinal or endocrine). We used a clinical score already published in the NEJM [12], which classifies the patients in terms of probability of chronic TAPOS. Points were given according to the presence of each item: erythema migrans (+5), positive B. burgdorferi serology (+5), tick-bite (+3),...
several organ categories of signs and symptoms (+2), only one organ category of signs and symptoms (+1). The sum of points gave a score allowing classification of patients according to the clinical probability of chronic TAPOS (little probable: less than 5 points, probable: from 5 to 9 points, very probable: more than 9 points). Patients were treated with an antibiotic effective against *B. burgdorferi* for at least three months. When the clinical condition was not clearly improved at month 3, the antibiotic course could be prolonged to six months. All data was collected in the Epi-Info 2000 software and statistical analysis was made by the PhEMI Center (Pharmaco-epidemiology applied to Infectious Diseases, INSERM) at the Pasteur Institute in Paris.

3. Results

3.1. Patients characteristics

One hundred patients were included among those who consulted during the study period for suspicion of chronic Lyme disease. The sex ratio was 0.35 (65 women and 35 men) and the average age was 45.1 years (CI 95: 42–48). The most frequently reported symptoms at the time of inclusion were neurological (94%), articular (91%), systemic (88%), and cutaneous (76%). This clinical pattern corresponds to published clinical data after infection by the *Borrelia* subspecies present in Europe.

3.2. Signs and symptoms at inclusion

The prevalent general signs at inclusion were asthenia (83% of cases), fever (36%), weight gain or loss (35%). They were generally associated with organ involvements, mainly neurological, psychiatric or cognitive, articular or cutaneous. Neurological symptoms were present in 94% of cases:

- paresthesias (83%);
- headaches (63%);
- neuralgias (39%);
- visual disorders (47%);
- auditory disorders (30%);
- ataxia (38%).

Neuropsychological signs or cognitive impairment were:

- mood disorders (39%);
- depression (7%);
- memory disorders (44%);
- concentration disorders (47%);
- sleep disorders (44%).

Articular signs were present in 91% of patients:

- poly-arthritis (83%);
- recurrent localized arthralgia (56%);
- arthritis (12%).

Cutaneous signs were present in 76% of patients:

- a history of chronic erythema migrans (53%);
- recurrent erythema migrans (16%);
- nonspecific erythematous plaques of chronic evolution (26%);
- aphthosis (16%);
- chronic pain at the tick-bite site (14%).

Cardiorespiratory signs and symptoms were present in 73% of patients:

- arrhythmia (52%);
- thoracic pain (41%);
- effort dyspnea (25%);
- chronic cough (11%);
- recurrent pharyngitis (20%);
- rhythm disorders (13%);
- arterial hypertension (11%).

Muscular signs and symptoms were present in 67% of patients:

- myalgia or flu-like syndrome of cyclic evolution (65%);
- muscle fasciculation (17%).

Gastro-intestinal symptoms were present in 47% of patients:

- epigastric pain (25%);
- or intestinal disorders (diarrhea, constipation or both) (26%).

Thyroid disorders were reported in 4% of patients.

We considered for the analysis that objective signs included:

- heart conduction and rate disorders (registered on electrocardiography);
- arterial hypertension, mono or oligo-arthritis;
- temporal and space disorientation;
- neurological deficit;
- hearing or visual disorders;
- chronic erythema migrans;
- galactorrhea;
- dysthyroidism;
- aphthosis;
- adenomegaly;
- fever.

3.3. Clinical score

A history of *erythema migrans* was found in 53% of the patients, *B. burgdorferi* serology was positive in 51%, a history of tick-bite in 69%, and the combination of several organ categories of suggestive symptoms in 82% for more than four organ categories, 10% for four, and 8% for three associated organ categories. Among the 100 patients, 67 were classified as “very probable”, 27 patients as “probable”, and six patients “little probable”.

3.4. Antibiotic treatment

The most frequently used antibiotics were amoxicillin (39%), ceftriaxone (31%), doxycycline (27%), clarithromycin (4%), and more rarely penicillin G (1%) or tinidazole (2%).

3.4.1. Evolution under antibiotic treatment

Of the 100 patients included in the study, 96 were evaluated at month 3 and 68 at month 6 after the beginning of antibiotic treatment. The evaluation performed at each medical visit (month 3 and month 6) showed a decrease in the number and intensity of signs and symptoms under antibiotic treatment (Fig. 1).
number of organ categories for signs and symptoms presented by the patients declined during the antibiotic treatment period: the percentage of patients presenting with more than four organ categories decreased from 82% at inclusion, to 39% at month 3, and to 31% at month 6.

3.4.2. Evolution of the signs and symptoms according to the organ category, their objective or subjective nature, and to the clinical score of chronic TAPOS

This evolution was evaluated in the subpopulation of patients whose follow-up was extended to month 6. Among these 64 patients, 43 presented with “very probable”, 16 “probable” and five “little probable” chronic TAPOS. The average age and the sex ratio of this subpopulation were not significantly different from those observed in the general population of the study. In the “very probable” group, the reduction of number of signs and symptoms was observed for each organ category. However, neurological signs and symptoms were the least improved during treatment. On the other hand, systemic, articular and cutaneous symptoms appeared more susceptible to antibiotic treatment (Fig. 2). The evolution of these two types of signs and symptoms under antibiotic treatment was evaluated separately. The
“very probable” group had a steeper slope of decrease for subjective symptoms (Fig. 3). The average number of objective signs also decreased in time under antibiotics, with a steeper slope for patients with a “very probable” diagnosis of TAPOS (Fig. 4). We observed a clear decrease of objective signs and subjective symptoms under prolonged treatment with antibiotic, with a stronger effect between inclusion and month 3, especially in the groups of patients classified as “probable” and “very probable”. No case of clinical aggravation or serious adverse event was reported in the three groups. Although this data was not prospectively recorded, around three-quarters of our study patients experienced an exacerbation of signs and symptoms during the antibiotic treatment, with a stronger slope of decrease for subjective symptoms (Fig. 3). The average number of objective signs also decreased in time under antibiotics, with a steeper slope for patients with a “very probable” diagnosis of TAPOS (Fig. 4). We observed a clear decrease of objective signs and subjective symptoms during the antibiotic treatment, either early acute reactions typical of Jarish-Herxheimer syndrome, or later subacute reactions. Exacerbation of signs could last several weeks or even several months in some patients, with the possibility of cyclic evolution. The difference between slopes of either objective signs or subjective symptoms between inclusion and month 3 was not significant in the “little probable” group, but was highly significant in the “probable” group ($p = 0.002$ and $p < 0.001$, respectively), and in the “very probable” group ($p < 0.001$). The most significant difference was observed in the decrease of objective signs between inclusion and month 3 among patients classified as “very probable”.

4. Discussion

Chronic Lyme disease is often considered in case of long-lasting symptoms after a tick-bite, but there are few descriptive epidemiological studies on the clinical presentation and the evolution in the course of time under prolonged antibiotic treatment [22–25]. This syndrome is not well defined, hence its pathophysiology is unclear and probably not due to only B. burgdorferi infection. We think that the denomination chronic Lyme disease is not appropriate and should be replaced by chronic TAPOS. In this prospective study of 100 patients, consulting for chronic TAPOS, the analysis of population epidemiological characteristics and symptoms presented bring new data on some poorly documented concepts. The definition of a clinical diagnostic score permitted the description and comparison of evolution under treatment of three categories of patients. The main objective of this study was to describe a population presenting with TAPOS and to help the clinician improve his diagnosis and therapeutic management by using a probability score. The antibiotics used varied according to the prescribing physician. One can thus regret a lack of uniform choice of medication. The descriptive analysis of our population gave a sex ratio of 0.35 (35 men for 65 women). Classically the sex ratio is close to one, compatible with the mode of vectorial transmission [26,27]. There is no obvious explanation for the high prevalence of women in our study. There may be a genetic or hormonal influence on the occurrence of Lyme disease tertiary phase. Are women more likely to develop post-infectious, autoimmune, or inflammatory symptoms? [28,29]. The average age of this adult population was 45 years, which corresponds to the second peak of Lyme disease. There are two peaks of frequency for the disease, the first between five and nine years and the second between 45 and 60 years. Our patients were young. Inflammatory or autoimmune diseases are frequent at this age range. A positive history of tick-bite was found in 69% of the patients, corresponding to published data [30]. Several explanations can be suggested: an unknown tick-bite (on a invisible zone, or tick-bite at the nymph stage), or forgetting the bite. The tick-bite (on a invisible zone, or tick-bite at the nymph stage) or cross-reactions with autoantibodies such as EBV infections, bacterial endocarditis, Ehrlichia and Babesia infections. False-negative results are also frequent. There is no reliable serological test in Europe and Asia due to heterogeneity of B. burgdorferi subspecies. In the early phase, serology is often negative and after a period of positivity, may become negative.
In the family life and often return to work. Various hypotheses on the duration of the antibiotic treatment were tested, but these results are contradictory. The number of patients receiving the treatment and the type of treatment vary greatly from one study to another. In Europe, the official recommendation for laboratories is to give a negative result for Borrelia serological test if the level of antibodies is under the ELISA threshold, even if the Western blot is highly positive.

PCR detection techniques for Borrelia DNA in various tissues is currently the most specific technique, but lacks sensitivity and specificity. In our study, the most frequently used antibiotics were beta-lactams (mainly amoxicillin and ceftriaxone, penicillin G in a few cases) and doxycycline, which correspond to the drugs currently recommended [32,33]. Clarithromycin was also used [22,34]. A few patients received tinidazole which was proved effective in vitro against cystic forms of Borrelia [16,18]. In our study, the frequency of neurological symptoms was more important than that of arthritic symptoms. In Europe, the known subspecies (Borrelia garinii and B. afzelii) have a preferential neurological tropism [4,35]. Contrary to the United States, where the isolated species (B. burgdorferi sensu stricto) cause pure arthritic symptoms, there were no isolated arthritic presentations in our study [36]. The patients in our cohort presented with various “poly-organic symptoms” and a quasi-constant general impairment (asthenia, anorexia, depressive syndrome). Many symptoms attributed to a late phase of Lyme disease are subjective. Thus, the few signs objectified by the clinician have a great diagnostic value. Some disturbances, seldom described in this disease, were noted in our study. Thyroid disorders were found in 4% of the patients. This frequency could be related to autoimmune mechanisms, with multiplication of Borrelia in the thyroid gland [37,38]. In addition, chronic arthralgia was observed in 16% of our patients. Approximately half of the patients of our study presented with memory, sleep, concentration, libido, and mood disorders deteriorating their quality of life. It is difficult to determine whether these disorders were due to a direct Borrelia attack in the brain in the primary and secondary phases, or to a depressive syndrome caused by a chronic disease which is painful and invalidating. The frequency of headaches (63%) among patients without history of migraine, associated with neck rigidity (44%) can evoke the existence of a chronic pseudo-meningitis syndrome after a tick-bite. The 100 patients included in the study received from three to six months of antibiotic treatment. No patient experienced severe adverse effects linked to treatment. Only some benign side effects were listed, such as cutaneous rashes, gastro-intestinal disturbances, or taste impairment. The symptoms whatever the diagnostic probability, decreased progressively. The effect of the antibiotic treatment was more important for articular and cutaneous signs, whereas neurological signs were apparently more permanent. The treatment was not fully effective, since only 4% of the patients considered themselves “cured”. Improvement was limited in 60% of the patients. This treatment, even if it did not cure all the patients, led to improvement of quality of life, with reinsertion in the family life and often return to work. Various hypotheses can be suggested for the failure frequency of antibiotic therapy. It could be due to insufficient dosage (poor intracerebral or intra-tissue penetration), route of administration or insufficient length of course. The persistence of symptoms after treatment can suggest a secondary autoimmune reaction with antibody over response against Borrelia or a general chronic inflammatory disease after bacterial aggression [28,29]. Another hypothesis is the existence of co-infection by one or more microorganisms such as Babesia, Ehrlichia, Anaplasma, Bartonella, Mycoplasma, Chlamydia, Brucella, Rickettsia, Coxiella, viruses such as the tick-born encephalitis (TBE) virus or HHV6. Some of these pathogens may be co-transmitted at the time of the tick-bites [39–41]. The partial lack of antibiotic efficacy could also be due to the capacity of Borrelia to escape the bactericidal effect of antibiotics as cystic forms. The cyclic conversion of cystic forms in free spirochetes could release new Borrelia in tissues [16,18]. The cyclic evolution was noted clinically for 28% of the patients in our study and could correspond to bacterial multiplication cycles. Psychiatric or cognitive symptoms were the most difficult to treat. The central nervous system, altered in an early phase, could be a sanctuary site, quiescent forms less accessible to antibiotic treatment [19,20]. Exacerbation of signs and symptoms during antibiotic therapy and the course of this exacerbation has not been well studied in the chronic forms of Lyme disease. These exacerbation phenomena may impede the evaluation of clinical improvement and could be partly responsible for the negative results of antibiotic treatment in chronic Lyme disease reported in several articles. The rather good results observed by Donia in the treatment of chronic Lyme disease when combining hydroxychloroquine to a macroclide antibiotic could be due, to an anti-infectious action of hydroxychloroquine in addition to the possible immunomodulatory effect of hydroxychloroquine [22,34].

Hydroxychloroquine is effective against parasites such as Babesia, and is also able to enhance the bactericidal activity of antibiotics within leucocytes, as it was shown for Coxiella burnetii or Mycobacterium tuberculosis [42,43]. Moreover, Brorson and Brorson showed that hydroxychloroquine could exhibit a direct inhibitory effect against Borrelia Burdorferi [16,18]. Our patients presented with post tick-bite symptoms, often invalidating and diminishing their quality of life, the cause of frequent medical consultations. The patients, more often female, were sometimes regarded as having disorders of hysterical nature. Nevertheless, these disorders deserve a particular consideration. In our study we tried to demonstrate that medical management was effective on symptoms, especially for patients with a high probability of chronic TAPOS. We did not investigate co-infections. However cases of co-infections by other tick-transmitted diseases are more frequently described, maybe accounting for the limited improvements observed.

5. Conclusion

It was thus appropriate to perform a double-blind, randomized study, taking into account the pitfalls of previous studies, to confirm the antibiotic effect and to rule out a “white blouse effect” on chronic symptoms in the context of chronic TAPOS.
[44]. Although the present study may have methodological limits, it will certainly help in terms of feasibility, choice of inclusion criteria, and design of follow-up for a future randomized, double-blind study testing the efficacy of prolonged anti-infectious therapy versus placebo among patients presenting with signs and symptoms of chronic TAPOs.

References