Management of patients presenting with generalized musculoskeletal pain and a suspicion of Lyme disease

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Conduite à tenir devant un tableau polyalgique chez des patients adressés pour suspicion de maladie de Lyme

Management of patients presenting with generalized musculoskeletal pain and a suspicion of Lyme disease

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Résumé

La maladie de Lyme, causée par des bactéries du complexe *B. burgdorferi sensu lato*, donne lieu à des manifestations cliniques polymorphes pouvant toucher plusieurs organes tels que la peau, le système nerveux central ou les articulations. Depuis quelques années, des associations de patients et des médecins soutiennent l'hypothèse selon laquelle cette infection donnerait lieu à des symptômes polyalgiques chroniques, sous le terme de « maladie de Lyme chronique ». La fibromyalgie (FM) est une entité clinique caractérisée par une polyalgie diffuse évoluant de façon chronique avec un impact majeur sur la qualité de vie et le fonctionnement social et psychique. Dans cette revue, nous avons analysé les données existantes dans la littérature concernant les entités de syndromes douloureux associés à la maladie de Lyme (*Post Treatment Lyme Disease Syndrome - PTLDS*) ou aux piqûres de tiques (symptomatologie polymorphe post piqûre de tiques). Nous avons également analysé les données existantes concernant le diagnostic, la physiopathologie et le traitement de la FM. L'ensemble des données recueillies montre que le PTLDS a des caractéristiques très proches d'une FM post infectieuse. D'autre part, les patients se présentant en service de maladies infectieuses pour un dépistage de maladie de Lyme devant des symptômes polyalgiques chroniques après une piqûre de tique devraient également bénéficier d'un dépistage de la FM afin de permettre une prise en charge adaptée, dans laquelle l'antibiothérapie n'a pas sa place.

Abstract

Lyme disease is caused by bacteria of the *B. burgdorferi sensu lato* complex, and can give polymorphic clinical manifestations that can affect several organs such as the skin, the central nervous system, or the joints. In recent years, patients' associations and physicians have been supporting the hypothesis that this infection would manifest as chronic generalized musculoskeletal pain symptoms, named "chronic Lyme disease".

Fibromyalgia is a clinical presentation characterized by chronic generalized musculoskeletal pain with a major impact on quality of life and social and psychological functioning. We analyzed existing literature data on pain syndromes associated with Lyme disease (post-treatment Lyme disease syndrome) or tick bites (polymorphic symptoms after a tick bite). We also analyzed existing data on the diagnosis, pathophysiology, and treatment of fibromyalgia. Our review shows that post-treatment Lyme disease syndrome has characteristics very close to post-infectious fibromyalgia. On the other hand, patients presenting for Lyme disease screening because of chronic generalized musculoskeletal pain symptoms after a tick bite should also be screened for fibromyalgia to allow appropriate management. Antibiotics are not recommended here.

Introduction

Lyme disease was first discovered by the international medical community following the description of an epidemic cluster of pediatric inflammatory arthritis cases in 1977 in the city of Lyme, Connecticut, United States [1,2]. The causative agent of Lyme disease, a spirochete, was then identified in 1983 by William Burgdorfer and named *Borrelia burgdorferi*. When other species were identified, they were all grouped together and named *Borrelia burgdorferi sensu lato,* including *B. burgdorferi sensu stricto*, *B. garinii,* and *B. afzelii* [3].

The first article published on this pathogen reported that the bacterium was transmitted by ticks of the *Ixodes* genus and that it could be responsible for multisystemic manifestations (dermatological, articular, cardiac, and neurological) [3].

Over the past years several physicians in the United States, Europe, and France have advanced that many other symptoms could be due to a "chronic" infection caused by *Borrelia burgdorferi sensu lato,* without any identification of the bacterium with currently available diagnostic means [4,5]. Signs and symptoms reported by patients' associations and by several physicians, and attributed to Lyme disease, are mainly subjective and highly polymorphic manifestations such as asthenia, concentration disorders, and generalized musculoskeletal pain [6]. No large-scale study has so far reported a causal relation between active infection caused by *Borrelia* and such symptoms [7]. However, a growing number of patients are consulting infectious disease specialists for chronic painful symptoms and ask for Lyme disease diagnostic tests.

Infectious disease specialists are therefore facing patients for whom they are lacking diagnostic and therapeutic tools: on the one hand, patients mainly present with subjective symptoms and infectious disease physicians are unsettled as they are used to base their clinical thinking on measurable objective signs such as fever, or on any other obvious abnormalities observed at physical examination; on the other hand, the etiology and treatment of these symptoms are currently poorly defined. No large-scale study has indeed been performed with this highly heterogeneous cohort of

patients presenting with a suspicion of Lyme disease because of generalized musculoskeletal pain symptoms.

Fibromyalgia is a chronic and widespread idiopathic musculoskeletal pain syndrome, named like this in 1977 − same year as the Lyme disease description. It has been officially recognized by the World Health Organization (WHO) in 1992. Substantial progress has been made over the past 10 years in its diagnostic criteria and treatment principles, which are now better codified. It is now well-known that fibromyalgia is highly frequent as it is believed to affect at least 4% of the general population, with a female to male ratio of 9-1 [8]. Infectious disease specialists should thus consider this diagnosis when confronted with patients presenting with generalized musculoskeletal pain symptoms.

We aimed to summarize literature data on generalized musculoskeletal pain symptoms related to Lyme disease and to detail available data on the definition, diagnostic tools, and treatment principles of fibromyalgia to improve knowledge and screening during infectious disease consultations. Current treatment options for fibromyalgia may also be tested for other generalized musculoskeletal pain symptoms, whether or not related to Lyme disease.

I. Generalized musculoskeletal pain symptoms related to Lyme disease and tick bites

"Post-Lyme" or "Post-treatment Lyme disease" syndrome (PTLDS)

This generalized musculoskeletal pain syndrome is currently the most consensual and the best described. The 2006 guidelines of the French Infectious Diseases Society (French acronym SPILF) define PTLDS as follows: "the association of asthenia, diffuse pain, and cognitive signs after an adequately treated Lyme disease" [9]. The SPILF guidelines clarify that this syndrome is wrongly called "chronic Lyme disease" as the active infection is never confirmed in such patients. The Infectious Diseases Society of America (IDSA) also defined "post-Lyme disease syndrome" in 2006: association of asthenia, diffuse musculoskeletal pain, and cognitive difficulties for at least six months within six months following antibiotic therapy for Lyme disease. The IDSA also mentioned that these symptoms may be severe and impact the patients' social and professional life. It is also clearly

mentioned that a confirmed and adequately treated Lyme disease is a prerequisite for the definition of this syndrome. This definition is also used by various European guidelines [10–16]. Several clinical trials have thus been conducted to assess PTLDS. Its prevalence is estimated at 5-15% of patients who have been treated for Lyme disease in the United States [17]. The most recent study of the prevalence of PTLDS was performed in 2015 [18]. Weitzner *et al.* prospectively assessed for more than 10 years a cohort of 128 patients presenting with erythema migrans confirmed by the identification of *Borrelia* in culture media. Overall, 10% of these patients presented with signs compatible with PTLDS and only 5% had persistent signs at the last study visit [18].

As for the clinical description of this syndrome and its potential determinants, Bujak *et al.* performed a study in the United States in 1996 to determine the clinical and cognitive characteristics of patients defined as having PTLDS [19]. A total of 23 patients met the PTLDS criteria: 30% received a fibromyalgia diagnosis, 13% a chronic fatigue syndrome diagnosis, and 43% presented with similar symptoms to both of these conditions but milder, preventing any official diagnosis to be established. In 2018 the same authors assessed sleep quality in PTLDS patients [20]. They prospectively assessed sleep quality using approved scores (Pittsburgh Sleep Quality Index), in a cohort of patients diagnosed with erythema migrans (n=122) versus healthy controls (n=26). Sleep quality was assessed on Day 0, immediately after erythema migrans treatment, and then at one year in the subgroup of patients who then presented with clinical criteria of PTLDS associated with a quality of life composite score (SF-36) below 45. Results highlighted that patients had poorer sleep quality at the erythema migrans phase than healthy controls. However, the difference was no longer observed after treatment. Only six patients met PTLDS criteria at one year post treatment (4%), and they had poorer sleep quality than the 10 healthy controls, as adjusted on age and sex. PTLDS patients also presented with pain, functional effects, and increased fatigue as compared with controls.

The benefit of an antibiotic therapy for patients presenting with PTLDS has long been discussed in the literature. Four randomized, double-blind, placebo-controlled clinical trials have

been performed and their results have been discussed and reinterpreted at length in the literature. However, these four randomized placebo-controlled studies reported similar results.

The first study was performed by Klempner *et al*. in 2001. They randomized 129 patients already treated for Lyme disease and meeting PTLDS criteria [21]. These patients had either a positive serology or a history of erythema migrans with a negative serology. A total of 64 patients received 30 days of intravenous (IV) ceftriaxone followed by 60 days of doxycycline, and 65 patients received an IV and then oral placebo for the same duration. The primary endpoint was the SF-36 score. An interim analysis was performed on Day 180 and revealed a calculated probability of 3.9% of observing a difference between both of these groups, when informing inclusions and study duration. The study thus had to be discontinued for futility. Over the study period the frequency of adverse effects was also higher in the antibiotic therapy group than in the placebo group [21]. It should also be noted that a substantial proportion of patients receiving the placebo (36%) significantly responded to treatment as per the primary endpoint.

The second study was performed by Krupp *et al.* in 2003. They studied the effectiveness of an antibiotic therapy with ceftriaxone versus placebo for 28 days, as assessed by the outcome criteria of fatigue (Fatigue Severity Scale, FSS), psychomotor impairment (A-A test), and *Borrelia* Osp antigen detection in cerebrospinal fluid (CSF) [22] in a cohort of 55 patients meeting PTLDS criteria. Fatigue improvement was observed at one month in both groups, without any difference. However, fatigue improvement only persisted at six months in the ceftriaxone group. No improvement in psychomotor impairment was observed [22]. An improvement of 0.5 point at the FSS score was observed in the placebo group, close to the significance threshold of 0.7 defined by the authors. Four patients also presented with severe adverse effects during the study period, including one presenting with anaphylaxis and three with IV line-related infections. The authors concluded to a negative overall benefit-risk ratio of the antibiotic therapy in patients presenting with PTLDS.

The third study was performed by Fallon *et al.* in 2008. They compared 37 patients meeting PTLDS criteria (with objective criteria of memory deficits assessed on the WMS III scale) and

randomized to either receive ceftriaxone or a placebo for 10 weeks [23]. The primary endpoint was the improvement of neurocognitive functions as assessed by various scales, with a total of eight endpoints. Twenty healthy controls were also evaluated using the same criteria over the same time period. The authors only reported an improvement in memory deficits in the ceftriaxone group at Week 12, but this improvement was no longer observed at Week 24. No conclusion could therefore be reached. However, the small sample size of the study and the numerous endpoints probably increased the α risk, as suggested by the comment of Klempner *et al*. on this study [24].

The most recent study was published in 2016 by Berende *et al.* in the *New England Journal of Medicine* [25]. They performed a randomized, double-blind, placebo-controlled study to assess the benefit of a 12-week antibiotic therapy in patients meeting PTLDS criteria with either a history of erythema migrans or of confirmed symptomatic Lyme disease and with at least one positive serology for IgM and IgG. All included patients had previously received 15 days of IV ceftriaxone. The primary endpoint was the SF-36 physical quality of life composite score at treatment completion, and the secondary endpoints were the other components of the SF-36 scale as well as a fatigue score. A total of 280 patients were randomized into three groups: one group receiving a placebo, one group receiving 12 weeks of doxycycline, and one group receiving a combination of clarithromycin and hydroxychloroquine for 12 weeks. No significant difference was observed between the groups.

The only studies concluding to the benefit of the antibiotic therapy in patients presenting with PTLDS unfortunately present many biases preventing to reach a conclusion. For instance, Horowitz performed a study of 100 patients presenting with a history of erythema migrans or with a positive serology for Lyme disease [26]. All patients received a combination of at least three antibiotics for one to four months, among the following: minocycline, doxycycline, rifampicin, atovaquone-proguanil, artemisinin, hydroxychloroquine, dapsone, or oral third-generation cephalosporins. Treatment effectiveness was self-assessed by patients using quantitative scales for measuring symptom severity from 0 to 4. Results of this study cannot be interpreted considering the

numerous biases caused by the variety of treatments used, the lack of a control group, and the numerous symptoms assessed.

Some data sets are available on the non-antibiotic treatment of PTLDS. D'adamo *et al.* performed a pilot study of eight patients who benefited from a mild resistance exercise intervention. The primary endpoint was musculoskeletal pain and quality of life of patients presenting with persisting symptoms three months after Lyme disease [27]. Results suggested an improvement in quality of life and decreased pain after the resistance exercise intervention. No adverse effect was reported.

Lantos *et al.* performed a literature review of the various "alternative" treatments used by patients presenting with PTLDS or labeled as "chronic Lyme disease" patients [28]. They reported more than 30 "unorthodox" treatments, mainly advertised and sold on the Internet. These treatments belonged to five therapeutic classes: oxygen therapies (hyperbaric oxygen therapy, hydrogen peroxide, ozone), energy and radiation-based therapies (ultraviolet rays, laser, saunas, electromagnetic waves), chelation and heavy metal therapies, nutritional therapies (vitamins, mug wort, fish oils, etc.), non-antibiotic pharmacological therapies (cortisone, urine ingestion, cholestyramine, stem cell transplantation, etc.). The authors observed no scientific evidence of efficacy for all five treatment categories in the literature [28]. They also reported that some of these treatments may lead to severe adverse effects.

2. Persistent polymorphic symptoms after a tick bite

The French High Council for Public Health (French acronym HCSP) suggested the following definition for the condition coined "persistent polymorphic symptoms after a tick bite". The condition is characterized by multiple subjective symptoms reported by some patients, mostly women, in the months following a tick bite. These subjective symptoms are asthenia, concentration disorders, and "brain fog" feeling. They may be associated with thinking disorders, migrating peripheral articular pain, neuropathic pain, and digestive or functional urinary signs (non-exhaustive list) [29].

In 2008, before this definition was drafted, Clarissou *et al.* suggested using the French acronym SPOT standing for "multiple organ syndrome associated with a tick bite" [30]. The authors performed a preliminary prospective non-randomized study with 100 patients actually meeting PTLDS criteria. All patients had already been treated with the recommended antibiotic therapy for Lyme disease and presented with asthenia, psychomotor impairment, multiple muscular, cardiac, cutaneous, or articular subjective symptoms [30]. This study concluded to the efficacy of a 3- to 6-month antibiotic therapy in alleviating symptoms, but it presents many biases preventing from standardizing those conclusions. Various molecules were used: amoxicillin for more than a third of patients, ceftriaxone for 30% of patients, or doxycycline or macrolides for the remaining patients. The authors did not perform any subgroup analysis to detect efficacy differences between treatments, which is possible. Assessing the efficacy considering the mean number of symptoms presented by patients may suffer from a lack of standardization. Treatment duration was left to the physician's judgment, until "symptom improvement".

This cohort of patients presenting with persistent symptoms after a tick bite seems highly heterogeneous, and no large-scale high-quality study has so far been conducted to recommend a specific treatment option.

III. Definition, diagnostic tools, and treatments of fibromyalgia

1. Definition

1.1. Screening and diagnosis

Fibromyalgia presents as chronic musculoskeletal pain, with the "asthenia, non-restorative sleep, cognitive disorders" triad and numerous functional, polymorphic, and dysautonomic symptoms affecting various organs (digestive tract, urinary tract, skin, eyes, ear, nose, and throat, etc.). This generalized musculoskeletal pain syndrome is characterized by the persistence of these signs for more than three months, with an almost permanent asthenia and random pain migration with an alternating of chronic pain and more acute pain [31, 32]. Pain may be spontaneous, triggered or intensified by external factors such as emotions, stress, the weather, or inadequate efforts [33]. Pain

is originally dysfunctional. It cannot be relieved with usual analgesics [34]. It may be complicated by comorbidities such as anxiety and depression, sleep disorders, temporomandibular joint dysfunction [35]. Fibromyalgia is responsible for stress and physical deconditioning, and is associated with an increased cardiovascular risk and with a risk of overweight [36]. When concomitant with migraine, fibromyalgia is a risk factor for suicide [37]. Consequently, this disease significantly impairs the patient's quality of life [38]. Diagnosis is first based on anamnesis and physical examination. No biological or radiological marker is available.

Screening is performed using the FIRST questionnaire [39] (Table 1). A cut-off score of five positive items out of six allows the detection of fibromyalgia with 90.5% sensitivity and 85.7% specificity [39]. In 1990 the American College of Rheumatology (ACR) suggested using the following diagnostic criteria: diffuse pain for more than three months, affecting the whole body, without any lateralization, and triggered by an 18-point finger pressure. The fibromyalgia diagnosis is established with at least 11/18 points. In 2010 the ACR suggested using a modified score including asthenia, sleep disorders, cognitive disorders, and functional symptoms. These new criteria combine a widespread pain index (WPI) between 0 and 19 (painful areas reported by patients) and a symptom severity sore (SSS) between 0 and 12. A global score called PSD (poly-symptomatic distress) is suggested; it combines the WPI and SSS scores [40]. The diagnosis is established when the following scores are observed for more than three months: WPI $\geq$7 and SSS $\geq$5 or WPI 4-6 and SSS $\geq$9 or WPI and SSS $>$12.

When the modified score started to be used, any other diseases potentially responsible for the observed symptoms had to be ruled out to establish fibromyalgia. This has become obsolete since the official recognition of the fibromyalgia type due to a specific disease (multiple sclerosis, rheumatoid arthritis, cancer, post-infectious disease, etc.) [41].

1.2. History and current context

Chronic painful disorders without any underlying organic conditions and without any explanations have been reported since the Antiquity. Following Charcot's works, fibromyalgia was

first considered in France as related to “functional disorders”. It remained classified as a psychosomatic disorder until the end of the 1970s, without having been extensively assessed. Following the use of the term *“*fibrositis*”* in 1904, suggesting the presence of muscular inflammatory lesions that have never been observed, two Canadians, Smythe and Moldofsky, coined the term “fibromyalgia” in 1977, which is now used worldwide [42]. This new term is, however, as unsatisfactory as the French acronym SPID (for diffuse idiopathic musculoskeletal pain syndrome) suggested by Kahn, but refused by the international scientific community [43].

Fibromyalgia was officially recognized by health authorities, such as the WHO in 1992, and the American College of Rheumatology approved its diagnostic criteria in 1990 [40]. The WHO attributed a specific CIM10 code (M 79.7) to fibromyalgia in 2006 and classified it among conjunctive tissue and musculoskeletal diseases. It has since been assessed by various study groups: the French National Academy of Medicine in 2007, the French National Authority for Health (French acronym HAS) in 2010 [31], and the French Parliament in 2016 [44]. The French National Institute for Health and Medical Research (French acronym INSERM) is currently writing a report on fibromyalgia. The European League Against Rheumatism (EULAR) published guidelines on the management of fibromyalgia in 2016 and updated them in 2017 [45].

1.3. Socio-economic impact of fibromyalgia

Fibromyalgia is believed to affect more than 4% of the population [46], with a ratio of almost nine women per one man [8]. The disease is mainly observed in middle-aged women, although pediatric presentations are observed and the few affected men present with a more severe form. Fibromyalgia is highly incapacitating. It has major impact on the patient’s professional life, with a risk of social exclusion [47], and it is costly to society [48]. Up to 30% of patients report not being able to keep on working after receiving a fibromyalgia diagnosis [49]. It is a poorly recognized disease lacking effective management. This was highlighted in a study reporting that family physicians only establish 0.2% of fibromyalgia diagnoses per year (i.e., three patients per year) versus 2.1% to 2.8% for

rheumatologists [50], neurologists, and internists. Patients first consult various specialists and the mean time to diagnosis is eight years [51].

1.4. Pathophysiology

1.4.1. Animal model

The pathophysiology of fibromyalgia is still not entirely understood.

Clauw and Sluka compared animal models with studies performed in humans. The mouse model consisted in repeated insults to the muscle (repeated non-inflammatory injections of acid into the limb), leading to autonomic generalized musculoskeletal pain with diffuse hyperalgesia and allodynia persisting in the absence of the initial stimulus, and associated with sleep disorders, asthenia, and anxiety and depression [52]. Overall, 80% of female mice versus 20% of male mice were affected; these proportions are similar to those observed in humans. Central and peripheral sensitization of the nervous system − although to varying degrees − was observed in both the mouse and human models, leading to multiple fibromyalgia symptoms [52].

1.4.2. Pathophysiological hypotheses

The etiopathogenesis of fibromyalgia is still disputed. Talotta *et al.* advanced that genetic predisposition, environmental triggers, and neuromodulation are all considered to be involved in the genesis and development of fibromyalgia [53]. A differential expression of more than 400 genes involved in the regulation of immuno-inflammatory, hypersensitivity, and allergic response pathways are observed in patients presenting with fibromyalgia as compared with healthy controls. A substantial differential expression of the leukocyte mRNA gene involved in mediators of nociception and

stress would allow to distinguish fibromyalgia patients from patients presenting with chronic fatigue syndrome [54]. Modifications in neurohormones involved in pain perception modulation (serotonin deficiency, increased substance P levels in CSF, increased glutamate levels in CSF and central nervous system) can be observed, as well as an abnormal metabolism of endorphins [53,57]. The strongest increases in glutamate brain levels were observed in the posterior cingulate cortex, the posterior

insula, the ventrolateral prefrontal cortex, and the amygdala of patients presenting with fibromyalgia and lowered pain threshold, fatigue, and impaired quality of life [53].

The role of pain neuromodulation in the pathogenesis of fibromyalgia has been extensively studied. Both the central and peripheral nervous systems are involved in pain hypersensitivity, although several authors tend to demonstrate the greater involvement of the central nervous system dysregulation at the spinal and supraspinal levels rather than peripheral small fiber dysfunction [53].

Hyperperfusion has been observed in hyperalgesia patients presenting with fibromyalgia in regions of the brain known to be involved in the sensory dimension of pain processing, and hypoperfusion in areas assumed to be associated with the affective-attentional dimension [55]. Increased connectivity has also been observed between the insula and the default mode network, as well as a decreased gray matter volume [56].

Increased NMDA nociceptive receptors associated with enhanced nociceptive responses and medullary reflex was reported. Increased excitability of the ascending tract is thus observed as well as decreased antinociceptive mechanisms of the descending inhibitory system. This phenomenon leads to increased chronic pain [33,52].

Increased levels of some amino acids with a neurotransmitter and neuromodulator action have been observed in patients presenting with fibromyalgia (alanine, glutamine, isoleucine, leucine, phenylalanine, proline, and valine).

High levels of corticotropin-releasing hormone (CRH) and substance P in these patients stimulate IL-1 and TNFα release from mast cells, acting as factors of pain hypersensitization [57]. Many studies reported low grade chronic inflammations (with normal CRP and ESR levels) and high levels of pro-inflammatory cytokines (IL-1Ra, IL-6, IL-8, TNFα) [53,58,59].

Studies have also demonstrated an increased size and innervation of arterio-venous shunts, an altered muscle oxygen consumption, and other abnormalities for which it is difficult to understand whether they are the cause or consequence of fibromyalgia [60].

Sleep disorders have also been reported, with a shorter total sleeping time, a shorter duration of slow-wave sleep, and more frequent waking bouts. Besides a probable impact on maintaining a certain level of fatigue, stress, and cognitive disorders, non-restorative sleep also impacts the sexual function [53].

At the functional level, these “microscopic” dysfunctions have behavioral “macroscopic” consequences. It has been demonstrated that patients presenting with fibromyalgia are less energetic than other people, with a lower and later activity peak during the day [61]. This decreased physical activity contributes to an overall deconditioning mechanism, acting as a vicious circle (Figure 1). Chronic pain and fatigue indeed impact patients’ behavior; they present with balance disorders, kinesiophobia, or dizziness and thus tend to reduce the amount of physical activity performed [38,62] (Figure 1). It has also been shown that these patients have impaired endurance with lower velocity at maximal oxygen uptake ($\dot{V}O_2$ max) and lower anaerobic ventilation threshold (SV1) [63].

1.5. Differential diagnoses

Before establishing a fibromyalgia diagnosis, and excluding secondary fibromyalgia associated with another disease, physicians should look for rheumatologic, autoimmune, infectious, endocrinal, oncological, or genetic diseases (Table 2) [64]. Even when the fibromyalgia diagnosis is established, all symptoms should not necessarily be assumed to be related to fibromyalgia: any new pain or changes in symptoms should be investigated.

Chronic fatigue syndrome is similar to fibromyalgia: asthenia for at least six months, unknown origin, non-alleviated with rest, and associated with more than 50% reduction in daily activities. Although fatigue is in that case the predominant symptom, it is associated with articular and muscular pain, sleep disorders, headaches, cognitive disorders, shivering attacks, pharyngeal pain, and cervical adenopathy. Besides their chronicity, both fibromyalgia and chronic fatigue syndrome are associated with poor susceptibility to pharmacological treatments. The sole difference between

these diseases are the symptoms presented (fatigue for chronic fatigue syndrome, and pain for fibromyalgia) and specific genetic backgrounds for each disease [54,65].

2. Approved treatment options for fibromyalgia

Recognizing the disease, the physical and psychological pain of patients, and consequences on their daily living is part of the treatment management, as well as learning how to use pharmacological and non-pharmacological treatments to relieve symptoms. The HAS recommends a multidisciplinary management with the following options [31]: physical exercise rehabilitation, cognitive behavioral therapy, use of adequate analgesics. In 2017 the EULAR confirmed this multimodal approach, with physical activity interventions as the primary recommendation [66].

2.1. Non-pharmacological management

Non-pharmacological treatments require the active involvement of patients, with or without a specialized physician. Best practice recommendations on non-pharmacological treatments have been issued and validated in France [67]. Adequate physical activity is recommended as the first-line treatment of fibromyalgia [45]. Physical activity is different from practicing a sport. It is defined as a muscle contraction leading to an increased metabolism as compared with baseline metabolism. The intensity, type, frequency, and duration of the physical activity should be adapted to the patient's tastes, physiological needs, and fitness. It can be performed at home, when commuting, at work, or during leisure time or sport [68, 69]. Physical activity is believed to act on the pain, function, and well-being of patients presenting with fibromyalgia. However, neither EULAR nor the HAS clearly mention the type of physical activity to perform [31,66].

Aquatic activities and combined activity programs seem to be more effective on the reduction of depressive symptoms and pain. Besides improvement in physical functions, physical activity seems to have a positive impact on specific quality of life after four months, on depression scores after six months, and on mean pain one year after the start of the exercise intervention [70, 71]. An impact on mood, fatigue, and often pain is observed immediately after the exercise session. In the worst

case scenario, if the session is adapted to the patient's need, pain usually does not get worse [71]. Further studies are required to clarify practice modalities and efficacy substrates of adequate physical activity [71, 72].

The French health act of January 26, 2016 − that came into effect on March 1, 2017 − associated with the 2017 departmental circular, mentions the possibility for family physicians to prescribe adapted physical exercises to patients presenting with chronic diseases [72–74]. However, fibromyalgia − for which physical activity is recommended − is currently not considered a chronic disease for social insurances in France.

Other non-pharmacological treatments used as part of a multimodal panel are: therapeutic education of patients on managing chronic pain; cognitive behavioral therapies for managing life rhythms, emotions, and stress; learning of body-mind techniques (self-hypnosis, sophrology, mindfulness meditation, etc.); hydrotherapy, counter stimulation techniques (physiotherapy, heat therapy, cold therapy, transcutaneous electrical nerve stimulation - TENS) [53, 72, 75].

Repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) are sometimes used because of their ease of initiation and tolerability, but their effect has never been proven on disability and on the short-term quality of life [75–78].

Comorbidities with a potential impact on chronic pain should be detected and treated: sleep apnea, temporomandibular joint dysfunction, bruxism, anxiety and depression, post-traumatic stress syndrome (PTSD). Social support is to be implemented if required.

2.2. Pharmacological treatments

The "drug prescription reflex" should be avoided as much as possible with patients presenting with fibromyalgia because drugs are poorly effective and associated with adverse effects. Drug treatments are not the best treatments for fibromyalgia, although they may be interesting to relieve symptoms, especially in case of comorbidities [31, 66]. The main drugs (antidepressants [tricyclics, selective serotonin re-uptake inhibitors], anti-epileptic drugs [pregabalin, gabapentin], analgesics [paracetamol, tramadol], etc.) are associated with poor or non-existent level of scientific evidence

[78]. The use of L-carnitine associated with physical exercise has been associated with a certain efficacy [79], just like ketamine treatment courses that may be punctually useful in pain management [80]. Topical treatments may also be used [81]. However, some drugs such as strong opioids, are not recommended because non-effective and associated with adverse effects [82]. Nonsteroidal anti-inflammatory drugs, corticosteroids, and benzodiazepines should also be avoided, except for comorbidities requiring their use.

Conclusion

This article is at the crossroads of the infectious disease and algology fields. It highlights the traps of excessive specialization and the value of a multidisciplinary approach with its precious sharing of knowledge [83]. Considering available data on fibromyalgia, one may wonder whether post-treatment Lyme disease syndrome described in Lyme disease should instead be considered as post-infectious fibromyalgia. Taking into account the prevalence and severity of fibromyalgia, patients consulting for chronic musculoskeletal pain symptoms with a history of tick bite without any biological evidence of Lyme disease (coined “persistent polymorphic symptoms after a tick bite” by the HCSP) should systematically be screened for fibromyalgia. Infectious disease specialists believe fibromyalgia and its non-pharmacological multimodal treatment options should be better explained to the various specialists and patients’ associations. This would probably prevent escalation in treatment prescription based on unjustified antibiotic therapies as their efficacy has never been proven on any of the pain syndromes associated with Lyme disease or tick bites. Patients presenting with fibromyalgia should be screened and assessed as early and accurately as possible to implement adequate customized treatment. The latest genetic advances could lead to better customized treatments.

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Figure 1. Le cercle vicieux du déconditionement physique de la fibromyalgie

(Adapté de la thèse de médecine de A.S Rouvière, 2017)

Figure 1. The vicious circle of physical deconditioning in patients presenting with fibromyalgia

(Adapted from A.S Rouvière's thesis, 2017)

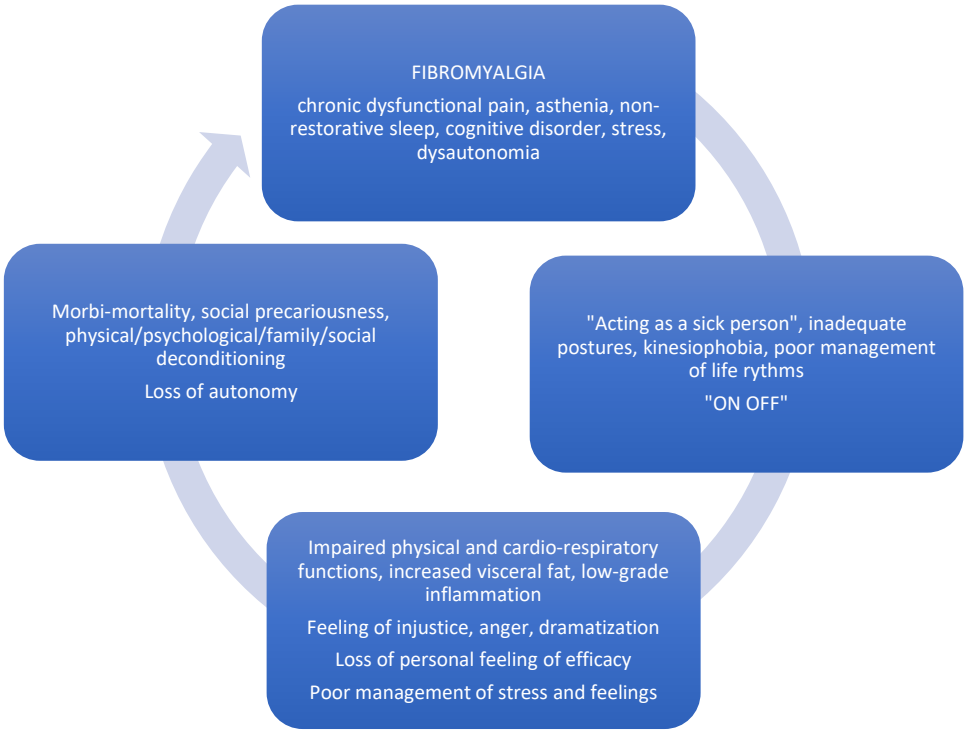

Table 1. FiRST screening questionnaire [39]
Tableau 1. Questionnaire de dépistage FiRST [39]

	For at least three months	Yes	No
1	Generalized pain (whole body)		
2	Pain is associated with chronic fatigue		
3	Pain feels like burns, electric shocks, or cramps		
4	Pain is associated with other abnormal feelings such as pins and needles, tingling, or numbness in the whole body		
5	Pain is associated with other health problems such as digestive disorders, urinary tract disorders, headaches, or restless legs		
6	Pain has a substantial impact on my daily living: mainly on sleep and concentration ability with the feeling of being slowed down		

Table 2. Some of the differential diagnoses of fibromyalgia [64]
Tableau 2. Quelques diagnostics différentiels de fibromyalgie [64]

Systemic and rheumatological diseases	• Rheumatoid arthritis • Spondyloarthritis • Arthritis • Joint hypermobility syndrome such as Ehlers-Danlos syndrome • Musculoskeletal syndrome • Scleroderma, LEAD, Sjögren syndrome • Myopathy and myositis • Celiac disease
Neurological diseases	• Multiple sclerosis • Myelopathy • Radiculalgia • Peripheral neuropathy
Endocrinal/metabolic diseases	• Hypothyroidism • Hyperparathyroidism • Hemochromatosis • Pernicious anemia
Infectious diseases	• Viroses (HBV, HCV, HIV, CMV, EBV, etc.) • Borreliosis
Psychiatric disorders and sleep disorders	• Mood disorders • Anxiety disorders • Post-traumatic stress syndrome • Substance abuse
Genetic disease	• Fabry disease
Oncological diseases	• Primitive oncological diseases • Paraneoplastic syndrome • Bone metastases
Other	• Chronic fatigue syndrome • Irritable bowel syndrome