

Lyme disease and persistent symptoms: a look at the current knowledge and recommendations for improving management

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

SUMMARY

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Introduction

The diagnosis of Lyme disease is complex, and the information circulating about this disease on various websites and social media platforms is not always consistent with the scientific data. The medical community is fundamentally divided over the possibility that Lyme disease may cause persistent, general systemic symptoms. In addition, there are still many concerns and uncertainties regarding the reliability of laboratory tests and the efficacy of antibiotic treatments. Regardless of these uncertainties, the presence of such persistent and often significant symptoms is a reality for many people and is the reason for a large number of medical visits and requests for laboratory tests or specialized examinations. Furthermore, some people struggling with such symptoms and looking for their cause step outside Québec's conventional healthcare system. They turn to clinicians who specialize in managing such patients, or they resort to tests performed by certain private laboratories and to different treatments, both pharmacological and nonpharmacological.

In May 2019, at the request of three branches of the Ministère de la Santé et des Services sociaux (MSSS), INESSS published clinical and implementation recommendations regarding the diagnosis, treatment and management of patients with localized or disseminated Lyme disease to equip health professionals, especially front-liners, given the increase in this illness. As a continuation of this work, MSSS asked INESSS to shed scientific light on the plausibility that Lyme disease can cause persistent, general systemic symptoms, on the contribution of laboratory approaches and tests to the diagnostic process, and on the benefits and risks of prolonged single and combined treatments and other treatment options, both pharmacological and nonpharmacological, that are suggested in such cases. A portrait of the care experience of patients with suspected or confirmed Lyme disease was also requested. All of this work was aimed at enabling INESSS to make recommendations for managing these patients.

Methodology

For the purposes of this task, INESSS conducted systematic reviews of the scientific literature and of publications containing positions, recommendations and guidelines on the subject. As well, contextual data and the perspectives of different stakeholders were gathered in order to document the issues important for patients, health professionals and the organization of services.

To gather the different perspectives, INESSS created an advisory committee consisting of clinicians, including medical specialists; experts in laboratory tests, acarological surveillance and public health; and patient partners with Lyme disease. In addition, clinicians with expertise in managing patients with persistent, general systemic symptoms attributed to Lyme disease were consulted through interviews or a survey to obtain the perspectives of clinicians with differing viewpoints. Consultations were also held with the head of the Manitoba's tick-borne collaborative care service and with the heads of three of France's five vector-borne disease referral centres. Further consultations were held with representatives from the Association québécoise de la maladie de Lyme and Enfance Lyme Québec, and interviews were conducted with patients with persistent, general systemic symptoms attributed to Lyme disease and with parents of children with such symptoms. The patient perspective was supplemented with case histories described in documents provided by patient associations and those mentioned by the various persons consulted. Lastly, a meeting was held with the coordinators and heads of Québec's four centres of expertise in chronic pain management to better understand models of care and service organization and to identify the barriers and facilitators of such structures in Québec.

To ensure that the recommendations intended for decision-makers and other stakeholders will suit the context of Québec, several committees collaborated on their development. This report reflects this exhaustive consultative process.

Results

The condition of certain patients with persistent, general systemic symptoms, which are constant or cyclical, is attributed to Lyme disease. Some of these patients have a history of confirmed Lyme disease (i.e., a diagnosis established with a high degree of certainty), while others do not.

Although many hypotheses have been put forth to support the plausibility that Lyme disease can cause persistent, general systemic symptoms, it is not possible from the current state of scientific knowledge to confirm or rule out a direct or indirect etiological role of bacteria belonging to the *B. burgdorferi s.l.* complex, or the role of concomitant infections, in the etiology of these symptoms. Learned societies are equivocal on the direct or indirect role that *B. burgdorferi s.l.* bacteria might play in the etiology of persistent symptoms, whether the patient has a history of confirmed Lyme disease or not. Health technology assessment agencies avoid expressing their opinion because of the lack of a clear definition of these patients' condition, or they propose a new clinical entity in which these bacteria are no longer considered the only possible etiological agents. The clinicians consulted are also divided over the possible role that *B. burgdorferi s.l.* bacteria might play in the etiology of persistent symptoms. Some endorse the likelihood of a certain persistent form of the infection, while others consider Lyme disease to be caused by other pathogens or concomitant infections, or they are more apt to believe that these patients have other conditions whose cause is not necessarily infectious or parainfectious. On the other hand, some clinicians mentioned the plausibility that infection by *B. burgdorferi s.l.* bacteria or other factors plays a triggering role that

results in a complex cascade of interactions that is the origin of the manifestations (e.g., autoinflammatory syndrome).

The serological tests used to complete the clinical picture in the context of Lyme disease appear to have significant limitations. In particular, they are dependent on the development of an immune response in the patient, and the commercial tests are not designed to detect all *B. burgdorferi s.l.* genospecies. None of the other laboratory approaches and tests examined during this work are specific to *B. burgdorferi s.l.* bacteria. While some provide information on the patient's immune system status, others provide information about the type of etiology, i.e., infectious or noninfectious. The systematic search of the scientific literature did not yield any studies evaluating their contribution to the diagnostic process in patients with persistent, general systemic symptoms attributed to Lyme disease.

Clinical trials of prolonged single or combined anti-infective therapies suggest that they have little or no efficacy for resolving persistent symptoms or improving quality of life. However, methodological limitations and the fact that all studies involved a heterogeneous population compromise the level of certainty regarding these results. In addition, only studies involving patients with a history of confirmed Lyme disease were identified during the systematic search of the scientific literature. Their conclusions are therefore difficult to generalize to all patients with persistent symptoms attributed to Lyme disease, since some of these patients do not have a history of confirmed disease. Different therapeutic approaches, both pharmacological and nonpharmacological, for relieving symptoms, preventing recurrences, boosting the immune system or treating an active infection are proposed in the literature, on special interest group websites and on various social media platforms. However, few of them have been the subject of a scientific publication concerning individuals with or without a history of confirmed Lyme disease.

Despite the scientific uncertainty regarding the etiology of the persistent symptoms and the diagnostic and therapeutic approaches to be used, our work revealed the following certainties:

- Knowledge about Lyme disease in Québec needs to be improved and consolidated in order to promote early diagnosis and management and thus prevent complications;
- The quality of life of adults and children with persistent, general systemic symptoms attributed to Lyme disease can be severely affected by persistent and sometimes very debilitating symptoms, which also creates challenges for the family members who provide care and support;
- These patients' care experience is often characterized by a long period of diagnosis-seeking;

- A diagnosis of Lyme disease may not have been considered or may have been erroneously dismissed in some of these patients (10 to 15%), but a different diagnosis should be made for most of the others following a thorough clinical investigation;
- Currently, management of these patients differs widely and is often fragmented;
- Dissatisfied with the response provided by Québec's healthcare system, some of these patients take action on their own to remedy their situation;
- As is the case for other complex and often chronic problems (e.g., fibromyalgia and chronic fatigue), the offer of service appears to be suboptimal and poorly integrated into Québec's health and social services system for patients with persistent, general systemic symptoms attributed to Lyme disease. Their needs are not easily met in the current organization of health services.

Management models of interest were identified, including one used in France. Beyond their names being associated with Lyme disease, France's referral centres offer, for complex cases, a thorough clinical investigation with no time pressure and the option of a supplemental multidisciplinary evaluation. Overall, these models promote patient management within the appropriate care channel and with individualized follow-up, regardless of the diagnosis made (infectious or noninfectious disease).

Conclusion

The review of the current state of scientific knowledge did not enable confirmation or ruling out that infection by *B. burgdorferi s.l.* bacteria can, directly or indirectly, cause persistent, general systemic symptoms, whether the patient has a history of confirmed Lyme disease or not. Nor did it enable ruling on the contribution of new laboratory approaches and tests to diagnosis or on the benefits and risks of prolonged single and combined anti-infective therapies in this context. The areas of uncertainty identified point to the need for research to better understand the etiology of these symptoms, to develop diagnostic tools and to identify efficacious and safe treatment regimens. Nevertheless, it emerges from the data gathered from various sources that patients with and without a history of confirmed Lyme disease experience a set of symptoms and incapacities for which the current healthcare system appears to offer few options. The improvement or even the development of a new offer of service for the target patient population could improve their access, fluidity and satisfaction in the care continuum.

Recommendations

In light of all the findings, INESSS has made four recommendations aimed at supporting the development and use of scientific and clinical knowledge and the improvement of the diagnostic and therapeutic management of adults and children with persistent, general systemic symptoms attributed to Lyme disease, whether they have a history of confirmed Lyme disease or not.

As a first step, given the consequences of a late diagnosis or the underdiagnosis of Lyme disease, INESSS reiterates, by way of a recommendation, the importance of raising awareness and knowledge of this disease among health professionals. A second recommendation has been made that is principally aimed at using the expertise developed by certain clinicians, particularly in the Eastern Townships and the Montérégie region, to support their colleagues who are less familiar with Lyme disease.

RECOMMENDATIONS REGARDING OVERALL IMPROVEMENT OF KNOWLEDGE AND EXPERTISE IN THE AREA OF LOCALIZED AND DISSEMINATED LYME DISEASE	CONSENSUS
<p>1. To continue the efforts to raise health professionals' awareness of the clinical manifestations of localized and disseminated Lyme disease and to ensure that treatments with proven efficacy can be offered as early as possible in the course of the illness:</p> <ul style="list-style-type: none"> • The professional orders, the federations and the associations concerned should develop and offer their members targeted training activities on these topics; and • Teaching institutions, particularly the faculties of medicine, pharmacy and nursing of Québec's various universities should ensure that up-to-date training is available to their students. 	Unanimous
<p>2. Structuring mechanisms should be put in place to strengthen second-line expertise and support front-line services for localized and disseminated Lyme disease. Agreed upon by MSSS and the medical organizations and professional orders concerned, these mechanisms could include promoting networking and peer support activities through an interprofessional and multidisciplinary collaborative platform (e.g., a community of practice).</p>	Unanimous

Secondly, given all the scientific uncertainty surrounding etiology of the symptoms and pathophysiology, and since a better understanding could eventually lead to improved diagnostic and therapeutic management of patients with persistent, general systemic symptoms attributed to Lyme disease, INESSS has made a recommendation aimed at raising the awareness of the Ministère de la Santé et des Services sociaux and the governance bodies concerned of the need to support research in this area. This recommendation also reaffirms the need for continued research on localized and disseminated Lyme disease, which was revealed in INESSS's initial work.

RECOMMENDATION FOR IMPROVING KNOWLEDGE OF LOCALIZED AND DISSEMINATED LYME DISEASE AND THE PERSISTENT, GENERAL SYSTEMIC SYMPTOMS ATTRIBUTED TO THIS ILLNESS	CONSENSUS
<p>3. Given the current state of scientific knowledge, every effort should be made by research governance bodies to support the scientific community, including clinicians, in the development and setting up of research studies that meet the standards of excellence and quality in order to:</p> <ul style="list-style-type: none"> • Permit the development of more sensitive and specific diagnostic tests for localized and disseminated Lyme disease and to generate evidence on the treatments available in such cases; • Document the profile of Quebecers with Lyme disease, whether or not the case meets the nosological definition used in the MADDO registry; • Better understand the pathophysiology in patients with persistent, general systemic symptoms attributed to Lyme disease and the possible clinical involvement of concomitant infections (tick-borne and opportunistic) or noninfectious etiologies (e.g., toxicology, autoinflammation and autoimmunity); • Create diagnostic tools and develop diagnostic approaches appropriate for the target patient population's health status; and • Identify efficacious and safe treatment regimens, notably by developing evidence to support therapies that are sometimes proposed on an empirical basis. 	<p style="text-align: center;">Unanimous</p>

Lastly, to improve the diagnostic and therapeutic management of the target patient population while at the same time facilitating the conduct of research projects and the reinvestment of acquired knowledge, INESSS has made a recommendation aimed at putting in place a structured offer of service for meeting these patients' needs and promoting synergy between research teams and clinicians.

RECOMMENDATION REGARDING THE OFFER OF CARE AND SERVICES FOR PATIENTS WITH PERSISTENT, GENERAL SYSTEMIC SYMPTOMS ATTRIBUTED TO LYME DISEASE	CONSENSUS
<p>4. To improve the care experience of patients with persistent, general systemic symptoms attributed to Lyme disease, to reduce diagnosis-seeking and to support the integration of research and clinical practice, MSSS should promote the implementation of an offer of care and services at one or certain designated referral centres, which would have particular important characteristics. More specifically, such centres:</p> <ul style="list-style-type: none"> • would provide a thorough clinical investigation based on a comprehensive diagnostic approach, with supplemental collaborative multidisciplinary evaluations when indicated; • would be created within a facility that has an academic mission and that is capable of conducting research and gathering clinical data in the real-world care setting; • would work in close collaboration with research teams in Québec, elsewhere in Canada and at the international level, conducting research on persistent, general systemic symptoms attributed to Lyme disease in patients with and without a history of confirmed Lyme disease; • would be accessible by adult and pediatric target patient populations (i.e., those with persistent, general systemic symptoms attributed to Lyme disease with or without a history of confirmed Lyme disease); • would promote interprofessional and multidisciplinary work and facilitate it using available technologies; • would promote the use of safe, evidence-based treatment regimens, where possible, and otherwise ensure that the offer of any investigational therapy is structured within a research framework; • would ensure continuity with medical, psychosocial and rehabilitation services based on the patient's symptoms, incapacities and unmet needs; • would support first and second line services throughout Québec by establishing a two-way exchange network and developing appropriate tools (e.g., tele-expertise services). 	<p style="text-align: center;">Strong majority</p>

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