

Tick-borne diseases: Challenge in diagnostics and therapies of chronic multiple infections

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Lyme-Borreliosis and coinfections are the chameleon of symptoms, laboratory test results and therapy options. Many patients can be infected by tick-bites with several bacteria (multiple infections). Symptoms of tick-borne diseases are not highly-specific for Lyme-Borreliosis or other coinfections (overlapping symptoms). The diagnostic approach should be done by modern and innovative laboratory tests with the highest sensitivity and specificity for each infection. The evasion from the immune system of pathogens plays an important role in the problems of diagnostic testing and therapies in the complexity of chronic multiple infections. Autoimmune disorders, many unexplained syndromes or cancer can be correlated with chronic multiple infections initiated by tick-borne diseases. This presentation aims to show symptoms and corresponding laboratory tests for tick-borne diseases, explaining the different diagnostic test systems and general therapy options for chronic multiple infections, respectively pathogen interactions and biofilms. Over recent years, a multitude of pathogens have been reported to be tick-borne. Given this, it is unsurprising that these might co-exist within the same tick, however our understanding of the interactions of these agents both within the tick and vertebrate host remains poorly defined. Despite the rich diversity of ticks, relatively few regularly feed on humans, 12 belonging to argasid and 20 ixodid species, and literature on co-infection is only available for a few of these species. The interplay of various pathogen combinations upon the vertebrate host and tick vector represents a current knowledge gap. The impact of co-infection in humans further extends into diagnostic challenges arising when multiple pathogens are encountered and we have little current data upon which to make therapeutic recommendations for those with multiple infections. Despite these shortcomings, there is now increasing recognition of co-infections and current research efforts are providing valuable insights into dynamics of pathogen interactions whether they facilitate or antagonise each other. Much of this existing data is focussed upon simultaneous infection, however the consequences of

sequential infection also need to be addressed. To this end, it is timely to review current understanding and highlight those areas still to address.

Classical forms of Lyme disease are usually easy to manage, but these medical conditions with pleomorphic nonspecific symptoms may prove confusing to physicians. Lyme disease may mimic chronic inflammatory or degenerative diseases, including a wide range of auto-immune diseases. Although practitioners from every medical specialty are likely to have encountered cases of Lyme disease, they may have failed to recognize it, no matter how skilled they are. A major obstacle is that only 30% of the patients report a history of tick bite and only 70–80% present with a primary erythema migrans, the pathognomonic initial lesion. Diagnostics and diagnosis, which are at the heart of the controversy surrounding tick-borne diseases, have different connotations. Diagnostics provide a cluster of objective measures directed toward identifying the cause of a disease. After scientists discover the causative agent of an emerging infectious disease, such as *Borrelia burgdorferi* or *Ehrlichia chaffeensis*, they develop, evaluate, and refine diagnostic tests over time. Diagnosis, by contrast, rests on a patient's history and symptoms and observed physical and laboratory findings. Ultimately, accurate diagnosis requires knowledge of the epidemiology, clinical manifestations, and diagnostic tests of a disease. Lyme disease presents a significant challenge to this standard approach. The presentation of symptoms may not align directly with the diagnostic laboratory test results. Necessary and sufficient conditions for the diagnosis may not be met, and yet the constellation of findings might lead one to make a diagnosis. At the time of acute presentation to a health professional, serologies may not be definitive. Conversely, serology may be positive, but symptoms may not match the serological picture. This suggests opportunities to develop laboratory measures that are reliable, valid, and sensitive to change and that may help to define the phases/stages of Lyme disease, such as acute, post-acute, chronic, and recurrent.