Is it Possible to Make a Valid Diagnosis of Lyme Disease Based on Symptoms Alone?

Lyme disease has been defined historically in the United States as a tick-borne infectious disease caused by a bacterial spirochete, *Borrelia burgdorferi sensu stricto* (1). It also has been called "the great imitator" because its symptoms are said to resemble those associated with several unrelated medical conditions. However, the fact that there are more than 350 medical conditions with symptoms very similar to those often attributed to Lyme disease (2), renders it extremely difficult – if not impossible— to make a valid diagnosis of Lyme disease based on symptoms alone, even in situations where the diagnosis of Lyme disease might seem to be most likely. For example, individuals living in endemic areas and exposed to ticks may develop a "bulls-eye" or *erythema migrans* (EM) rash that may be sufficiently pathognomonic for Lyme disease to justify antibiotic therapy with no additional testing; however, such a rash is present in 70-80% -- not 100%-- of those who acquire Lyme disease, and is sometimes mistaken for other types of skin reactions (3, 4). Although some consider the appearance of facial palsy a hallmark feature of Lyme disease, it is sometimes expressed in patients with other medical conditions, including several common viral infections (5). Even in regions where Lyme disease is endemic, 3 of 4 facial palsies are unrelated to Lyme disease (6).

Annual surveys by the Centers for Disease Control and Prevention (CDC) indicate that about 15% of women and 10% of men in the general population of the United States felt exhausted or extremely tired (fatigued) either every day or most days of the preceding 3 months (7), and that about 16% of men and 22% of women experienced pain in the past 3 months (8). It is estimated that nonspecific irritable bowel symptoms affect about 11% of the general population (9). Subjective cognitive decline (SCD) is a form of impairment in which more frequent or worsening confusion or memory loss can affect the ability to care for oneself. Among adults aged $\geq$ 45 years, 11.2% reported SCD, including 10.4% of adults aged 45-54 years (10).The Institute of Medicine (IOM) reports that nonspecific chronic pain affects 100 million Americans, about 30% of the general population; such individuals go from one physician to another, unable to find anyone who can identify the cause of their pain or suggest a remedy (11). Thus, individuals who believe that they have "chronic Lyme disease" might well be included in all of these cohorts, simply based on the presence of symptoms that are widely prevalent in the general population.

Some strongly assert that the diagnosis of Lyme disease is a "clinical judgement". Although this term can mean different things to different people, it is generally meant to be a judgement based on the results of a large body of evidenced derived from peer-reviewed research, i.e., evidence that is generally accepted by well-informed physicians in the medical community at large. To date, a PubMed search of the scientific literature reveals more than 12,000 publications dealing with practically every aspect of Lyme disease.

Since its discovery in the United States in the mid-1970s, we have learned a great deal about the cause, diagnosis, and treatment of Lyme disease. It is not the strange and mysterious disease that some imagine it to be, nor is it a disease without a cure. A physician who is board certified in the specialty of infectious diseases is certainly "Lyme literate" and should know how to diagnose and successfully treat Lyme disease; so should general practitioners in endemic areas with much experience treating patients with Lyme disease. Lyme disease conforms to the same fundamental rules and principles that apply to other infectious diseases. This likewise applies to the host immune response to *B. burgdorferi* and/or its various cell surface antigens. There are no "special rules" that apply only to Lyme disease, and one does not need to acquire "special training" or insights in medical school -- or anywhere else for that matter—

just to learn how to diagnose and treat Lyme disease. Although there is abundant knowledge upon which to base a rational clinical judgement, the results of an approved and correctly performed objective laboratory test certainly are invaluable in making and/or confirming the validity of a diagnosis of Lyme disease.

The accuracy and reliability of two-tier testing, which has long been accepted as the standard procedure for the laboratory diagnosis of Lyme disease, has been discussed in great detail (12, 13); however, there is much false and misleading information about its development and use. For example, it is often stated that the criteria used for the interpretation of Western blots used in the second step of the two-step procedure were selected arbitrarily. Instead, they were based on the results of a rigorous statistical analysis of Western blots for 225 case and control subjects revealing 8 IgM bands associated with early infection, and 10 IgG bands detected 4-6 weeks after infection (14). When receiver operating characteristic (ROC) curves, which are plots of sensitivity *vs* specificity, were constructed for the most common IgM bands detected in early disease, as well as for the most common IgG bands detected after several weeks of infection, the area under each optimal ROC curve indicated that the minimum number of bands required to obtain 99% specificity, was at least 2 for IgM bands, and at least 5 for IgG bands; this gave the greatest incidence of unequivocal positive values in combination with the lowest incidence of false positive values (14). These objective findings provide the foundation for the criteria recommended by the CDC for Western blots now being used in two-tier testing for Lyme disease (13). Note that recombinant proteins now have replaced undefined whole-cell sonicates as ligands in Western blots; this has not only increased sensitivity and precision, but also has considerably reduced intra-laboratory variation in the results obtained.

Comparisons were made between the results obtained using the standard two-tiered test procedure *vs* those obtained using ELISA tests performed with whole-cell sonicates (WCS) or different well-defined and highly specific peptides (C6 or VlsE) as ligands (15). They showed that, in assays of specimen samples collected 4-6 weeks or longer after infection, there was complete agreement in all cases, thereby confirming the reliability of standard two-tier testing done late after infection (15). However, for comparisons made using specimens from patients with acute EM and during early infection, greater sensitivity (25-50%) was noted for ELISAs using the defined ligands than for ELISAs using whole-cell sonicates (16-38%). Since Borrelia replicate (divide) at a slow rate (once every 12 hours), it may not be possible to realize much greater gains in sensitivity and earlier detection of antibody; obviously, it simply takes time for sufficient antibodies to be generated by the host immune system in response to Borrelia antigens, even when these extremely sensitive methods are used for the detection of the small amount of antibody produced (12). The results of other comparative studies also suggest that the use of two ELISAs conducted with defined ligands (C6 and VlsE) give results comparable to those obtained using the conventional two-tier procedure. Although this suggests that the use of two ELISAs using defined ligands might obviate the need for doing Western blots (15), additional studies are needed to establish that point.

A major disadvantage of using Western blots is that the results obtained are qualitative, rather than quantitative in nature. The use of quantitative ELISAs and specific peptides as ligands should enable one to distinguish between high levels of serum antibody that are characteristic of active infection from the low levels of background antibodies often detected in patients cured of infection. In this context, low levels of background antibody often persist for several years after an infection has been cured by antibiotic therapy; this makes it difficult to distinguish between active infection and past exposure by

means of Western blots (12). The use of quantitative ELISAs should be more fully evaluated for routine use, since ELISA plate readers with relevant software have been commercially available for many years at low cost.

A second major misconception about two-tier testing is the notion that its reliability is no better than that of "a coin toss" (16). This false claim is due to misinterpretation of the results obtained early after infection -- at the time an EM is present -- when sensitivity is indeed at or less than 50%; in contrast, the situation is quite different 4-6 weeks after infection by which time the full array of Borrelia specific antigens is expressed and antibodies specific for most – if not all—of these antigens can be detected in blood. There is ample evidence to indicate that individuals infected for 4 or more weeks in duration – unless immunocompromised—are seropositive by the CDC IgG Western blot criteria (12). Therefore, one must seriously question whether individuals who claim that they have suffered from Lyme disease for long periods of time or years and are seronegative by two-tier testing, really have Lyme disease. Even the most specific and sensitive diagnostic test for Lyme disease that one can imagine will not give a positive result for an individual who does not have Lyme disease.

A third major misconception is the view that the post treatment symptoms that some patients experience after receiving recommended treatment for Lyme disease (PTLDS) , are due to a persistent infection termed "chronic Lyme disease" that requires longer antibiotic therapy with other kinds of antibiotics -- given singly or in combination-- to cure. It should be noted that the results of five placebo-controlled clinical trials on the efficacy of extended antibiotic therapy for the treatment of PTLDS, provided no evidence of a persistent infection in such patients by culture and/or other laboratory tests; the results of all of these clinical studies showed no significant lessening of symptoms which one would expect to occur if such symptoms were due to a persistent infection (17-20). Furthermore, most seronegative individuals who believe that they have "chronic Lyme disease" seldom – if ever—have evidence of a persistent infection by culture or any other laboratory test.

Some believe that reports indicating the ability of Borrelia survive antibiotic treatment *in vitro* mimic what occurs *in vivo* during "chronic Lyme disease" and suggests the likelihood of a persistent infection in patients previously treated with antibiotics. However, such *in vitro* studies fail to compensate for the protective effects attributed to the host immune system *in vivo*. More important, there is no evidence that such *in vitro* findings have any clinical relevance (21). The presence of antibiotic resistant "persisters" may very well be an *in vitro* laboratory artifact that can be explained by basic biochemical kinetics since the ability to detect "persisters" *in vitro* is influenced greatly by both the numbers of Borrelia and concentration of antibiotics used (22).

In view of these considerations, what is the "take home message" for those who believe that they have Lyme disease based on symptoms alone, but are seronegative by two-tier testing? There are several that could have serious consequences:

First, in view of all that has been said above on the inability to make a valid diagnosis of Lyme disease based on symptoms alone, the recommendation to treat until symptoms disappear seems most unwise to say the least. It makes no sense to treat a patient with antibiotics for long periods of time in the absence of any tangible evidence of active infection.

Second, such patients often become victims of countless unorthodox remedies claiming to cure the Lyme disease that they do not have using unproven approaches with no demonstrable benefit that may

even be harmful (23). Often, this is done at great personal expense – sometimes for as much as $70K-$80K per year -- since health insurance companies will pay only for remedies known to be beneficial and safe for the treatment of correctly diagnosed illnesses. Obviously, it would not be in the best interest of the public health to pass legislation requiring health insurance companies to pay for unorthodox remedies of no proven benefit. That would increase the costs of medical care for all, making it even more difficult for those who can least afford it to obtain the medical care they need.

Third, the fixation on Lyme disease -- and only on Lyme disease -- as the sole cause of their symptoms prevents one from seeking medical advice to consider other possible causes for their symptoms. When correctly diagnosed and treated, such symptoms often can be resolved promptly, with an almost miraculous return to normal good health.

Fourth, the dissatisfaction resulting from the use of unproven unorthodox procedures for the treatment of Lyme disease, as well as the dissemination of much false and misleading information on the internet and in the media, have generated much dissatisfaction and distrust. Unfortunately, many competent scientists and physicians, who have just the expertise needed to address issues related to Lyme disease have become the targets of such negativity (24). To make matters worse, a concerted effort is being made to discredit the recommendations made by the Infectious Diseases Society of America (IDSA) in its guidelines for the treatment of Lyme disease (3). These guidelines are universally accepted by experts on Lyme disease throughout the world, and the treatment recommended has been demonstrated to be both beneficial and safe (24). No other set of guidelines has been subjected to such independent and intense scrutiny and critical review -- and survived the process intact with no revisions recommended (25). Quite simply, if we chose to abandon the rational and disciplined approaches historically associated with the scientific enterprise and the practice of medicine, then all we are left with is magic and superstition to solve our problems.

The IOM published a comprehensive report advocating a multidisciplinary rational approach for dealing with chronic pain and other nonspecific symptoms that occur in the general population and that often are incorrectly attributed to Lyme disease (11). Its recommendations make good sense and deserve to be given serious consideration and implemented.

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