PERSPECTIVES IN LYME BORRELIOSIS

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SUMMARY

The principles of an automatic pattern recognition and classification methods are explained. A neural network (NN) is a computing structure, its purpose is to get input data and return some kind of output. This task is not performed by means of an algorithm, but rather learnt by the network itself by looking at a certain number of examples (training set). NN offers the possibility of being trained by examples and exhibits a remarkable generalization power that lets these data to be correctly interpreted. Several applications of such systems have confirmed that they can be used to establish the diagnosis and to assess the prognosis.

KEY WORDS

Neural network, training set, generalization, establishing of diagnosis and prognosis, automatic pattern recognition

The entire history of Lyme borreliosis (Lb) is certainly not yet written. Further discoveries will allow to reorganize previously described but not yet correctly interpreted facts. The earliest cases of Lb were thought to have occurred 25 years ago on Cape Cod and in Connecticut. The spirochete has been identified in museum specimen ticks collected over 50 years ago.

Vectors, reservoirs and transmission cycles.

Knowledge of zoonotic transmission cycles is essential for the development of effective strategies for disease individualization and prevention. *Bb* is maintained in enzootic cycles involving wildlife hosts and ticks. In USA, *Ixodes dammini, Ixodes pacificus, Ixodes*

neotomae support an enzootic cycle that ensures presence of *Bb* in environment. In Europe, *Ixodes ricinus, Ixodes persulcatus* and *Ixodes hexagonus* may be infected with *Bb*. In USA, the preferred host for Ixodes dammini is the white-footed mouse; addle ticks feed on deer and other rodents; humans and birds may serve as vectors. In Europe it is generally assumed that mice and voles as well as some species of frequently grounded birds, serve as spirochetal reservoirs. Geographic differences in transmission cycles have been well established. Discovery of novel enzootic transmission cycle in California is an impressing example of new knowledge in this important field. Establishing the parameters of interactions between *Bb*, vectors and animal hosts is further challenge for future researchers.

Diagnosis.

Although knowledge of the epidemiology, clinical features, laboratory diagnosis and treatment of disease has greatly expanded in recent years, a definitive diagnosis of the late stage is often very difficult to obtain, if erythema migrans was either missed or absent. Persistent but vague chronic joint pain, fatigue, loss of memory, muscle weakness, or minor rheumatic complaints may be the only clues to the diagnosis of Lyme disease. Peripheral nerve palsy, atypical recurring arthritis claim for *Bb* serologic studies, but the absence of standardization of current tests is still a problem. Besides, many geographic diversities and different prevalence figures concerning clinical manifestations, especially for articular disease, which seemed to be more common in American than in European patients, represent further diagnostic problem. In endemic areas, high prevalence of antibodies against *Bb* can produce overdiagnosis. In many clinician's opinion the established diagnostic criteria are so narrow that they miss many people who are suffering from late Lb and would benefit from prolonged antibiotic therapy. Antimicrobial agents to which *Bb* is susceptible are efficient against many bacteria, and therapeutic trials are difficult to interpret. Serologic negativity for Ab against *Bb* (IFA or ELISA methods) in clinically confirmed borreliosis is another diagnostic problem in some cases. An element of qualitative judgment is involved in interpretation of Western blotting. Epidemiological case definition is intended for surveillance purposes only. In absence of erythema migrans, clinical diagnosis is still difficult. Current serodiagnostic techniques are of poor predictive value in diagnosing Lyme borreliosis in many indefinite articular and neurological complaints. Relatively high false-positive rates of 2 % or more were observed in most current serological assays. Probably the most frequent chronic non-specific symptoms are too vague to be helpful in confirming diagnosis. Flagellar antigen in ELISA improves the sensitivity of the methods. The PCR is being developed as a diagnostic tool to detect the presence of bacterial DNA. Attempts are also made to develop antigen assays to detect one or more bacterial proteins. An urine antigen assay has been available in North America, but was recently withdrawn by the company because of lack of specificity. At present, current serological assays have value only in clinical situations strongly suggesting Lyme borreliosis. Thus only patients with objective clinical abnormalities must be tested.

Automatic pattern recognition and classification methods.

Recent studies have shown that neural networks can be used to cover several significant aspects of clinical problems in diagnosing Lyme borreliosis, by combining generalization power for diagnostic accuracy with clustering capability for procedure formalization. Appropriate methodologies, provided that there is an adequate database for training, can yield good results in studying such a complex problem. Results show that the diagnostic performance is high if compared to the more traditional methods. Alternate automated methods for diagnosing Lb are used: advanced pattern classification techniques applied to the data established by medical observations. Neural network (NN) is a computing structure, its purpose is to get input data and return some kind of output. However, this task is not performed by means of an algorithm, it is rather learnt by the network itself by looking at a certain number of examples (the training set). NN offers the possibility of being trained by examples (i.e. learning a given data set) and exhibits a remarkable generalization power that lets new data, not included in the training set, to be correctly interpreted on the basis of the inner structure of the database which was learned during the training phase. Several applications of such systems have confirmed that they can be used to establish the diagnosis and to assess the prognosis. The structure endows it with appealing properties, such as absence of domain-specific explicit knowledge (as required by conventional expert systems), inherent domain-adaptiveness, and notable generalization power. Thus NN methodology is likely to

be suitable for solving clinical problems. Diagnosis is approached as a classification problem, in which a feedforward neural network learns sample patient descriptions and classifies unknown patterns accordingly. The standard training procedure (known as the back-propagation algorithm) requires the training set, including the class information (Ill/Non-Ill), to be repeatedly shown to a NN. Each time, an error is found in the output, which is the difference between the expected output value and the actual value obtained. This error is back-propagated through the network, and each unit corrects its input weights to minimize its own contribution to the total error. When the output error reaches a desired minimum (maybe 0), or stops decreasing, the training ends and a performance test can be made. Using 582 Lb pts as the training set, and 65 as test set, the ordered list of significant descriptors coincided with clinical expectation, including the presence of ECM or the progress of IgG among the most relevant indicators. The percentage of overall error averages approximately 8%, which appears quite satisfactory as compared to other automated or empirical approaches in diagnosing Lb. Neural networks can be used to cover several significant aspects of clinical problems in diagnosing Lyme borreliosis, combining generalization power for diagnostic accuracy with clustering capability for procedure formalization.

Manipulating phlogosis in Lyme arthritis.

80% of patients with ECM develop arthritis or arthralgias. Erosive, chronic arthritis is more frequently seen in patients HLA-DR4 or HLA-DR2/positive. Bb is potent inducer of IL-1 on synoviocytes and chondrocytes, while IL-1 is implicated in pathogenesis of inflammatory Lyme arthritis. The balance between IL-1 and IL-1 receptor antagonist might influence disease expression. A rapid resolution of attacks of arthritis was reported in patients with high concentrations of IL-1 receptor antagonist and low concentrations of IL-1 beta, whereas patients with the reverse pattern of cytokine concentrations needed long intervals to recover. Joint inflammation in Lyme disease patients can be successfully treated by blocking endogenous IL-1 activity. Studies using IL-1 receptor antagonist to block endogenous activity in a variety of animal arthritis models are reported. Strategies for reducing the effects of IL-1 have been based on suppression of transcription, translation or secretion; naturally occurring IL-1 specific receptor antagonist which shares 40% aminoacid homology with IL-1 beta, but does not possess agonist activity and acts as a competitive inhibitor of IL- 1, is a more recent approach.

Auto immune disease.

If Lyme arthritis may persist through a reactive mechanism or some other auto immune pathway, even in absence of living *Bb*, immuno-modulators may become a future alternative therapeutic approach.

Therapy of tick bites.

Ticks can be infected with several different pathogenic microorganisms, e.g. *Bb*, tick-borne encephalitis virus, and Rickettsia conori. Tick bites in areas which are endemic from *Bb* infections must be properly evaluated: the probability of Lyme disease ranges from about 0.012 to 0.05. If examination of the tick for borreliae is not possible, prophylactic antibiotic therapy as empirical treatment is suggested by Magid et al. only if the probability of infection ranges from 0.01 to 0.0035. A suitable rapid test for detecting Bb in ticks would be very useful prevention of Lyme disease after tick bites.

A Lyme disease vaccine.

Using a hamster model of Lyme disease, both active immunity and passive protection have been demonstrated. *Bb* Osp-A protein induces a good protection in rodents. A dog vaccine has been released for veterinary use. Therefore, a human vaccine is a reasonable though rather distant goal.

Education.

Educational instruments are needed to provide an appropriate response to popular demand for information on this important subject. Experts involved in Lyme disease research must be aware of this primary requirement and develop proper educational programs.

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