Decision Support for Diagnosis of Lyme Disease

Ole K Hejlesen, Kristian G Olesen, Ram Dessau, Ivan Beltoft, Michael Trangeled

Aalborg University, Aalborg, Denmark, Næstved Hospital, Næstved, Denmark

Abstract

This paper describes the development of a Bayesian model for diagnosis of patients suspected of Lyme disease, and the integration of such a model into a medical information system. A Bayesian network incorporating the clinical history and laboratory results has been constructed. Because many of the symptoms are not exclusive to Lyme disease and they develop over time, the clinical history is important for making the correct diagnosis. The model is based on time slices, where each time slice contains the observed pathological picture from one consultation with for example, the general practitioner. Since the time intervals between consultations typically are not equivalent, we have developed a novel method that can handle non-equivalent time intervals between the time slices in the network. The method is based on a description of the general development pattern of Lyme disease, which is implemented in a model that states the conditional probabilities of experiencing a certain pathological picture given time since infection. The model has been integrated into a web-based medical information system, called Borrelia Systems, which has enabled us to evaluate the model during a progressive diagnostic process. The integration has been accomplished through the development of a Bayesian Application Framework. This framework specifies a communication data structure in XML providing a graphical user interface and database components, which can be used when developing systems that are based on Bayesian networks. The framework generalizes the integration of Bayesian networks so that it is possible to switch network without manually having to update or change the system.

Keywords:
Lyme disease; Borrelia; Bayesian networks; Decision Support

1. Introduction

Lyme disease, or Lyme Borreliosis (LB), is the most commonly reported tick-borne infection in Europe and North America. The disease can affect many types of organs including the skin, nervous system, joints and in rare cases other organs. Lyme disease was named in 1977 when arthritis was observed in a cluster of children in and around Lyme, Connecticut, USA. Subsequent studies led to the isolation from the deer tick, Ixodes scapularis, of a gram-negative spirochaete, which was named Borrelia burgdorferi. These bacteria are transmitted to humans by the bite of infected ticks.

Lyme disease, or Lyme Borreliosis (LB), is divided into three stages, named early localized LB (stage 1, 2-30 days after initial infection), early disseminated LB (stage 2, few days - 3 months after initial infection) and late (chronic) LB (stage 3, from 3 months after initial infection). The stage of Lyme disease is decided from the symptoms that the patient is experiencing. In some cases the patient does not develop symptoms of a certain stage or the symptoms are not detected. Therefore, the patient does not always experience earlier stages
of Lyme disease. The duration of the stages also varies substantially from case to case and it is therefore difficult to determine the stage of the disease, even though the time since the bite is known.

It is important to make the correct diagnosis of Lyme disease in an early stage, because the complications in the later stages can cause irreversible injuries, if not treated with antibiotics. If Lyme disease of an early stage is diagnosed and treated, almost all cases will recover completely.

The symptoms of Lyme disease are not exclusive for Lyme disease, and it is therefore important to include all parameters when the diagnosis is made. These are the clinical findings, the clinical history, the risk exposure history, and laboratory evidence [1, 2].

**Clinical Findings**

*Erythema Migrans* (EM) (stage 1) is the most frequent clinical manifestation of LB and is found in approximately 60% of the cases with LB. EM is characterized by a red rash spreading from the site of a tick bite, as illustrated in Figure 1. The lesion evolves in a circular shape from the centre of the tick bite and out, and can reach from a few centimetres up to 75 cm in diameter. The incubation time is between 2-30 days after the tick bite with a median of 10 days. EM occurs at any age and in both sexes.

![Figure 1 - Erythema Migrans (EM)](image)

*Borrelial Lymphocytoma* (stage 2) presents as a bluish-red tumour skin infiltrate, up to a few centimetres in diameter, which may occur in some patients. The lesion may develop several weeks to months after a tick bite. The preferred sites are the ear lobe, ear helix, nipple or scrotum in children, and nipple in adults. The lesion may be preceded by EM or occur simultaneously with it. The lesion heals spontaneously but can persist and even grow for several months. Borrelial lymphocytoma is not found in North America.

*Acrodermatitis Chronica Atrophicans* (ACA) (stage 3) is a progressive skin condition that is most commonly found on the lower leg, but also the soles and palms, toes, fingers, and knees can be involved. The initial signs of ACA are a bluish discoloration and swelling of the skin. ACA does not heal spontaneously and if the patient does not seek medical attention, fibrous thickening may develop over, or close to joints, and after years of progression the skin lesion will gradually become thin shiny and papery.

*Early neuroborreliosis* (stage 2) is one of the clinical manifestations of Lyme disease that affects the nervous system and is also known as the Bannwarth syndrome. It affects all age groups with a median at the fifth decade. The incubation period of the Bannwarth syndrome is from few weeks to 2 months in adults, but shorter in children. The main manifestations are radicular pain, peripheral pareses and most often facial palsy. It begins with severe radicular pain that have been described as burning, tearing and migrating. The pain continues for approximately two weeks, but has been seen to last up to 25 weeks before complete recovery. Patients with radicular pain may experience depression, agitation, restlessness, sleeplessness, and anxiety. The majority of cases of early neuroborreliosis occur between July and November with the most cases observed in August.

*Chronic Neuroborreliosis* (stage 3) is very rare and should not be diagnosed without clear laboratory evidence of B. burgdorferi infection, because the symptoms could be caused by other non borrelia related manifestations as neurosyphilis, fungal meningoencephalitis and
brain tumours. The major manifestations of chronic neuroborreliosis are encephalitis, radiculomyelitis, transverse myelitis, stroke-like disorders and cranial nerve deficits. It can result in the patient having memory loss, depression, and spastic paraparesis.

*Lyme arthritis* (stage 2 and 3) is the major clinical manifestation affecting the joints. The knees are most often affected, together with other major joints as ankle, wrist and elbow. 50% of the cases of LB in North America develop arthritis posterior to untreated EM. The problem is not as common in Europe, which is thought to be because of the variations in the distribution of the different species of the bacteria in different parts of the world. Lyme arthritis may occur within several months after an unrecognized primary infection and last for several years. It affects most age groups, but is most likely found in the fourth decade, and older children are more affected than younger.

*Acute cardiac involvement* (stage 2) is a rarely observed manifestation. The symptoms are conduction disturbances and rhythm disturbances.

**Laboratory Evidence**

With the exception of typical EM, diagnosis of Lyme disease should always be confirmed by laboratory evidence. In clinical practice indirect methods of detecting borrelial infection is widely used. The method consists of determination of *IgM and IgG antibodies* by e.g. an enzyme linked immunosorbent assay test (ELISA). One of the major advantages of the ELISA test is its ease of use in large scale testing and the avoidance of subjective interpretation. Determining antibodies should be done with caution, as the correlation of results from different laboratories may be poor. This means that clinicians should understand the sensitivity and specificity of ELISA, and be aware of the predictive values for certain clinical manifestations.

A large proportion of the EM patients may have no antibody response. For all other clinical manifestations of LB, laboratory evidence of infection is essential for the diagnosis.

IgM antibodies directed against Borrelia burgdorferi antigens usually appear within three weeks of infection, and peak between four and six weeks post-infection, when IgG antibodies are also likely to be present. The IgG test can show negative until 2-3 months after the infection. The IgG level normally peaks after 4-6 months. Although antibodies tend to wane, they may remain detectable for months or years, with or without treatment, and serology has no role in measuring the response to treatment. The progress of the antibody response is illustrated in Figure 2. Not all patients follow this typical pattern.

![Figure 2 – Typical IgM and IgG development after infection](image)

**Epidemiology**

LB affects all age groups, but the rate of disease incidences is bimodal with the highest rates found in children less than 15 years of age and in adults older than 35 years of age, and there are slightly more males than females reported with Lyme disease. Disease incidence rates are increased in certain occupational groups, e.g. forestry workers, in some recreational groups such as orienteers and in tourists to high-endemic areas. The majority of the reported cases of LB experience disease onset in June, July, or August, which account for about 70% of the total number of reported cases, and with neuroborreliosis peaking approximately one month later in August.
2. Materials and methods

As described, the disease, i.e., its history, clinical manifestation, time course, serology, and epidemiology, is very variable and has a high degree of uncertainty. Bayesian networks are specifically suited to handle such problems [3, 4] and have also been used in earlier versions of our Borrelia model [5], which were however, not able to handle a history with repetitive clinical examinations. The present version of our system explicitly models the clinical history with one or more consultations with the clinician, and based on this information, it calculates the probability of Lyme disease. It should be noted that the present model is tuned to match the European variant of Lyme disease.

Figure 3 - The concept of modelling the clinical history by comparison with the general development pattern of Lyme disease over time

A normal procedure, when the diagnosis on Lyme disease is uncertain, is to ask the patient to return for a later examination in order to check if the disease develops as the typical pattern of Lyme disease. Thus, the clinical history is an important parameter when a diagnosis on Lyme disease is made and therefore, the Bayesian model also has to include the clinical history as one of its parameters.

The concept of modelling the clinical history is based on a description of the development pattern of Lyme disease over time. The development of Lyme disease begins at the time of the infection and then it progresses with the development of the different symptoms as time passes. The patient typically first discovers the infection some time after the bite incident and perhaps first when consulting the doctor. The concept of modelling the clinical history is to find out if the clinical findings at the time of the consultation match the general development pattern of Lyme disease. This concept is illustrated in Figure 3, where the horizontal axis represents the time, starting at the time of infection, and the vertical axis represents the probability of having a symptom (S) given that the patient suffers from Lyme disease, $P(S | L_d)$. The development of the stage 1 symptom Erythema migrans (EM) and the stage 2 symptom Lymphocytoma over time is shown: Typically, EM appears within a few days after the infection and is likely to be found up to one month after. The highest probability of observing EM is therefore, found in this period. Typically, lymphocytoma appears in the period from two weeks to two months after the infection, and the probability therefore peaks within this period. The concept of the development pattern illustrated in the figure, describes the probability of experiencing a time dependant variable at different times after the infection.

Figure 4 - The exposure risk history model

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First stage of the Bayesian model is the *exposure risk history* model, which can be seen in Figure 4. The arrows in a Bayesian model represent causal relations, and for example, the tick activity is dependant on the month of the year and the probability of a tick bite is dependant on the tick activity. Likewise, the patient’s ability to recall a tick bite is dependent on the actual occurrence of a tick bite. The two separate tick bite variables, Tick Bite and Tick Bite 2, is just a result of a design trick (‘divorcing parents’) helping to avoid too many dimensions in the conditional probability tables in the model. The other variables represent other epidemiological aspects described previously.

The following stages of the model are blocks of the *clinical findings and laboratory evidence model*, which can be seen in Figure 5. For example, it can be seen how a positive result of an IgM test can be caused by both a rise in IgM caused by Lyme disease (i.e. a true positive) and by other reasons (i.e. a false positive). Likewise an observed rash can be caused either by Erythema migrans (EM), which again is caused by the Lyme disease, or by other reasons. The conditional probability tables for the variables directly dependant of the Lyme disease variable, e.g. IgM and EM, are calculated dynamically by the method illustrated in Figure 3. The model can handle any number of clinical consultations as illustrated by Figure 6, where the blocks are connected by causal relations between the Lyme disease variables; i.e. the probability of Lyme disease at a given consultation is dependent on the occurrence of the disease in the previous block.

The model has been integrated into a system by developing a Bayesian Application Framework. This framework specifies a communication data structure in XML providing a graphical user interface and database components, which can be used when developing systems that are based on Bayesian networks. The framework generalizes the integration of Bayesian networks making it possible to switch network without manually having to update or change the system.

Both the model and the total system have been tested along commonly accepted guidelines proposed by Jeremy Wyatt and David Spiegelhalter [6] and by Jacob Nielsen [7]. The results are summarised in the following section.

3. Results

Two expert microbiologists tested the model behaviour with a single consultation and with
multiple consultations. The results show that the model with a single consultation, in general behaves as previous models. With multiple consultations it was concluded that the new time sliced model behaves as intended when the clinical history is incorporated. Also with an atypical course of the disease, the model in general behaves as expected.

The usability evaluation of the full system was performed by five general practitioners (GPs) who answered the 3 questions: ‘is it pleasant to use?’, ‘does it say sensible things?’ and ‘is it wanted?’ In general, the GPs found that the system is simple and has a good layout, and the layout was found to be logical and to have a good overview of the details. When entering different pathological pictures, the GPs in general found that the results were consistent with what could be expected, even though most of them found it difficult to evaluate an estimated probability of Lyme disease. In general, the GPs did not want a stand-alone system to handle Lyme disease, but suggested that the system, if it is to have any chance of success, has to be integrated into the general GP IT solution.

4. Discussion

From the analysis of Lyme disease it was evident that a decision support model for diagnosis of Lyme disease needs to incorporate the clinical history, which was not the case in previous models. Based on the evaluation of the present time sliced model it can be concluded that the method proposed for handling non-equivalent time intervals in order to incorporate the clinical history works as expected by expert microbiologists. Even though the general practitioners found that the system was pleasant to use, and was providing sensible information, they felt that the system in order to fit into daily routines, has to be integrated into their general IT systems. It is therefore concluded that in addition to more testing of the models performance on clinical cases, more work also has to go into improving the usability, i.e. the functionality in daily clinical practice.

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6. References


Address for correspondence

Ole Hejlesen, Ph.D., Associate Prof., Head of Med. Inf. Group, Dept. of Health Science & Technology, Aalborg Univ., Fredrik Bajersvej 7 D1, DK-9220 Aalborg, +4596358808/+4520459779, okh@hst.aau.dk.