T-cell response in Lyme disease (TRIL-study)

Published: 16-08-2011
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Main objective: To determine the T cell response to Borrelia specific antigens using an ELISpot interferon gamma release assay in patients with different clinical presentations of Lyme and healthy volunteers.Sub-question 1: QuestionnairesTo analyze...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON50284

Source
ToetsingOnline

Brief title
TRIL-study

Condition

- Bacterial infectious disorders

Synonym
Lyme disease/ Lyme borreliosis

Research involving
Human

Sponsors and support

Primary sponsor: Diakonessenhuis Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ELISpot, Lyme disease, T-cell response

Outcome measures

Primary outcome

Results of the Borrelia ELISpot assay and conventional two-tier serology for patients with Lyme disease and healthy volunteers.

Secondary outcome

1) Results of the Lyme-specific questionnaire and the health-related questionnaire (RAND-36)

2) Results of the specificity tests of:

-) the Borrelia ELISpot assay for patients with active disease known to cross-react with Borrelia such as syphilis, leptospirosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Helicobacter pylori, Mycoplasma pneumonia, rheumatoid arthritis (RA) or the presence of antinuclear antibodies (ANA)

-) the antibody tests on leptospirosis, Treponema pallidum and Helicobacter pylori for participants with Borrelia specific T cells in their blood and the controls (age and sex matched).

3) Results of the antiganglioside antibody test.

4) Results of the retrospective study in search for possible predisposing factors which can be helpful for clinicians in the decision-making of performing a lumbar puncture in case Lyme neuroborreliosis is suspected.

5) Results of the search for other factors (cytokines and/or immune cells and/or genetic polymorphisms) which might play a rol in the development of Lyme disease and the possible development of persisting complaints, which could be used for optimizing the ELISpot.

6) Identification of new immunological or genetic markers involved in the development of Lyme borreliosis and/or persisting complaints, in order to improve the diagnostics and therapeutic interventions for Lyme borreliosis, and the evaluation of these new tools.

7) Results of the evaluation of tests other than the ELISpot, which detect a response to the pathogen.

Study description

Background summary

Lyme is an emerging tick borne disease in the Netherlands with a high impact on public health caused by Borrelia spp. infected ticks of the Ixodes ricinus complex and can transmit the Borrelia spp. to humans. In Europe, Borrelia afzelii and Borrelia garinii are predominant, but B. burgdorferi sensu stricto can also be encountered. In North America, only infections with B. burgdorferi sensu stricto have been observed. The most common manifestation of Lyme is erythema migrans (EM). Other manifestations include radiculitis and arthritis although many people will clear the infection asymptomatically.

Diagnosis relies on the detection of antibodies against Borrelia spp.. Unfortunately these antibodies can persist a lifetime and therefore do not discriminate between active disease or cleared infection. Seroprevalence in the Netherlands has been reported to be as high as 15 % in risk groups such as owners of hunting dogs and 9% in controls (blood donors), 97% were asymptomatically infected (Nohlmans et al; 1991). No serological tests are available for differentiating between active disease or past infection.

The incidence of physician consults for tick bites and erythema migrans has tripled in the period between 1994 and 2009. It is very likely that the prevalence of complications of Lyme disease has also increased significantly. Due to the clinical heterogeneity Lyme is often considered by a clinician, this combined with the high background seropositivity results in that patients are often unnecessary treated. A diagnostic test which could differentiate between active disease and past infection would be very helpful for accurate diagnosis of active Lyme disease, but could also prevent unnecessary use of antibiotics.

T-cell mediated cellular immunity has a pivotal role in dealing with Borrelia spp. infection and subsequent clearance or control of the bacterium in the host. Using ELISpot techniques Borrelia specific circulating activated T-cells can be measured in the peripheral blood. After clearance of infection activated T-cells can disappear from the blood since active immune surveillance is no longer required. No studies are performed on determining T-cell responses in Lyme which may aid the clinician in accurately diagnosing the outcome of especially advanced stages of Lyme infection and might be useful in guiding therapeutic interventions. Using ELISpot techniques, it could be possible to differentiate patients with active Lyme from patients with a serological scar after Borrelia infection.

Study objective

Main objective:
To determine the T cell response to Borrelia specific antigens using an ELISpot interferon gamma release assay in patients with different clinical presentations of Lyme and healthy volunteers.

Sub-question 1: Questionnaires
To analyze the answers on the questions of the Lyme-specific questionnaire and the health-related questionnaire (RAND-36) to study the occurrence of tick bites, erythema migrans, antibiotic treatment for Lyme, complaints at the start of the study or during possible earlier episodes of Lyme and to investigate the quality of life of the study participants.

Sub-question 2: Specificity of the Borrelia ELISpot assay
-) To determine the specificity of the Borrelia ELISpot interferon gamma release assay by including patients with active disease known to cross-react with Borrelia such as syphilis, leptospirosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Helicobacter pylori, Mycoplasma pneumonia, rheumatoid arthritis (RA) or the presence of antinuclear antibodies (ANA) (=study group 5).
-) To test the presence of antibodies against closely related micro organisms such as leptospirosis, Treponema pallidum and Helicobacter pylori in participants who have Borrelia specific T cells in their blood (positive Borrelia ELISpot result). As controls, age and sexmatched study subjects will be selected who do not have Borrelia specific T cells in their blood (negative Borrelia ELISpot result).

Sub-question 3: Ganglioside antibodies versus complaints
To determine the presence of antiganglioside antibodies in all study subjects to see whether an association can be found between those antibodies and the persistence of complaints in treated Lyme patients.

Sub-question 4: Other cytokines and/or immune cells
To determine whether other factors (cytokines and/or immune cells) could possibly play a role in the development of Lyme disease and and/or persisting complaints in order to improve the Borrelia ELISpot technique.

Sub-question 5: Predisposing factors for Lyme neuroborreliosis
For the inclusion of Lyme neuroborreliosis patients the electronic patient records showed that not all presumed Lyme neuroborreliosis infections were confirmed and some patients were eventually diagnosed with other diseases such as neurosyphilis, Guillain-Barre, or had a hernia. Only 11% of all neuroborreliosis requests at the microbiology lab resulted in a Lyme neuroborreliosis diagnosis. Since lumbar punctures are very invasive, we want to investigate whether we can increase the likelihood of a positive Lyme neuroborreliosis diagnosis by retrospectively analyzing the electronic patient records of all patients who have had a lumbar puncture for the diagnosis of an infectious disease. Patient history (anamnesis), supplementary examination by a physician and other laboratory test outcomes will be analyzed in order to find predisposing factors. In a prospective study those factors will be tested in order to increase the likelihood of a positive test outcome and decrease the number of unnecessary lumbar punctures.

Sub-question 6: Genetic factors vs symptoms
To detect polymorphisms within the Borrelia bacterium and/or human cells (such as Toll-like receptor polymorphisms, HLA-polymorphisms, etc) which could be related to persisting symptoms after antibiotic treatment for Lyme borreliosis.

Sub-question 7: Validation of other tests and/or identification of new targets
a) To validate tests other than the Borrelia ELISpot, which detect a response to the pathogen.
b) To identify new targets for diagnostics and/or immunotherapy for Lyme disease. These new targets could include e.g. particular DNA sequences, proteins or lipids that can be used in the development of new diagnostic or therapeutic tools for Lyme disease.

Study design

Descriptive study, evaluation of a new diagnostic test.

Study burden and risks

All patients with active Lyme disease such as neuroborreliosis or Lyme

arthritis who undergo treatment at the Diakonessen hospital in Utrecht or St Antonius hospital Nieuwegein/ Leidsche Rijn are elligable. Those patients will undergo full history and physical examination.

All participants will fill out a standard questionnaire measuring general health (RAND-36) and a Lyme specific questionaire and will be subjected to a single blood sampling. No specific risks are associated with any aspect of the study.

All participants selected for determining the specificity of the Borrelia ELISpot by testing their blood on the presence of antibodies agaist leptospirosis, Treponema pallidum and Helicobacter pylori have to sign an additional informed consent. Positive test results will be reported back to the participants, which can have an impact on them. They will therefore be offered more information and/or a consultation with a clinician.

This will be offered in case of:
-) positive Lyme serology in case of healthy volunteers
-) positive Borrelia ELISpot results in case of healthy volunteers and treated Lyme patients
-) positive serology in case of leptospirosis, Treponema pallidum and Helicobacter pylori for the selected participants

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- 20 persons with positive Lyme serology who have no symptoms of Borrelia infection
- 20 persons without Lyme symptoms and negative Lyme serology
- 50 patients treated for Lyme disease such as acute Lyme neuroborreliosis
- 125 patients with active Lyme disease such as acute Lyme neuroborreliosis
- 10-20 patients/disease, consisting of patients with active disease known to cross-react with Borrelia such as syphilis, leptospirosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Helicobacter pylori, Mycoplasma pneumonia, rheumatoid arthritis (RA) or the presence of antinuclear antibodies (ANA).
- informed consent

Exclusion criteria

* immunosuppressive medication
* < 18 years

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-03-2012
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO Date:	16-08-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	12-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL36407.100.11