LymeProspect: a prospective study into the longterm-effects of Lyme borreliosis and determinants for persisting symptoms

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Primary objective: To assess microbiological, immunological, genetic, clinical, cognitive-behavioral, and epidemiological determinants for development of persisting symptoms in both adult and juvenile Lyme patients, and establish prediction rules *...

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

Summary

ID

NL-OMON47035

Source
ToetsingOnline

Brief title
LymeProspect

Condition

- Bacterial infectious disorders

Synonym
Borrelia infection after tick bite, Lyme disease

Research involving
Human

Sponsors and support

Primary sponsor: RIVM

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Borrelia burgdorferi, Lyme disease, Tick-borne disease

Outcome measures

Primary outcome

The main study endpoint is whom of the confirmed Lyme patients develop persisting symptoms, based upon the validated symptom and disability questionnaires.

The main study parameters are all microbiological, immunological, genetic, clinical, cognitive-behavioral, and epidemiological parameters measured during follow-up of these confirmed Lyme patients, that possibly predict development of such persisting symptoms, i.e.:

-Quantitative PCRs for Borrelia on skin and blood samples

-typed Borrelia cultures from skin samples, and minimal inhibitory concentrations (MICs) for relevant antibiotics, as well as molecular typing of cultivated Borrelia burgdorferi subspecies

-PCRs for other tick-borne pathogens on skin and blood samples

-Antibiotic trough levels in blood samples collected during standard antibiotic treatment in all clinical Lyme center patients

-Borrelia C6 ELISA (IgM/IgG; Immunetics) and both a IgM and IgG immunoblot (Mikrogen) and serology for other tick-borne pathogens in blood samples.

-Cellular immune responses: ex-vivo stimulation of whole blood and (fresh) PBMCs - collected before and after antibiotic treatment with Borrelia and other stimuli.

- Four cellular tests (Spirofind® (Oxford Immunotec), QuantiFERON Lyme® (QIAGEN), the EliSpot assay developed by AID (Autoimmun Diagnostika GmbH) in Strassberg, Germany) and the LTT-MELISA (developed by Invitalabs in Neuss, Germany) before and after antibiotic treatment. The tests are based on the ex vivo stimulation of blood (whole blood or PBMCs) with Borrelia according to the manufacturers protocol to examine the specific cellular immune reactivity to B. burgdorferi s.l and to assess whether test results are related to clinical outcome.
-Gene expression arrays: we will perform micro-arrays (Illumina) using RNA from frozen peripheral blood mononuclear cells (PBMCs) * collected before and after antibiotic treatment * that are ex-vivo stimulated with Borrelia and other stimuli.
-Humoral immune response: IgG2/IgG1 ratios in patients before and after treatment in search of an activity marker.
-Complement cascade: Mannose Binding Lectin (MBL) levels before and after treatment
-All relevant outcomes of the questionnaires that possibly predict development of persisting symptoms.

Secondary outcome

Secondary study parameters are all microbiological, immunological, genetic, clinical, cognitive-behavioral, and epidemiological parameters as described above * but now in the unconfirmed Lyme patients with existing persisting symptoms * that are possibly similar to the determinants of such persisting

symptoms that were identified in the confirmed Lyme patients.

Study description

Background summary

In the past 15 years, a three-fold increase in the number of tick bites and cases of Lyme borreliosis has been observed in the Netherlands, with currently more than one million tick bites and 20.000-30.000 Lyme borreliosis cases per year. 20-30% of all tick bites and Lyme borreliosis is attributed to children.
The majority of Lyme borreliosis patients respond well to antibiotic treatment but around 5-20% of patients report persisting symptoms such as musculoskeletal pain, neurocognitive symptoms and fatigue. These persisting and sometimes disabling symptoms can have great impact on the quality of life.
Currently it is not known to what extent long-term persisting symptoms are related to persistence of Borrelia infection, auto-inflammation or auto-immunity, co-infection with other tick-borne pathogens, or other mechanisms. In the proposed study, we will prospectively investigate the clinical course of antibiotic-treated Lyme borreliosis and assess the actual risk of developing persisting symptoms. To assess specific determinants for development of such symptoms, we will include microbiological, immunological, genetic, clinical, cognitive-behavioral, and epidemiological explanations for these symptoms in the measurements during patient follow-up.
Children may well have different risks and/or determinants to develop persisting symptoms than adults. Since such differences would call for specific diagnostic and treatment strategies for children, the risk and determinants of persisting symptoms with Lyme borreliosis should be assessed specific for children and for adults.
Furthermore, no other prospective studies have been performed to persisting symptoms after Lyme borreliosis in children. Several differences between children and adults for acute Lyme manifestations that may well be related to different risk and determinants of persisting symptoms have been described. The inclusion and prospective follow-up of children in this study allows us to look specifically for determinants that predict for development of persisting symptoms for individual children.
Our study is unique and innovative by its prospective and holistic approach. The prospective follow-up of patients allows us to identify determinants that predict the development of persisting symptoms for individual patients, both for children and for adults. The results of this study will thus contribute to future treatment strategies that prevent or resolve persisting symptoms in individual Lyme borreliosis patients.

Study objective

Primary objective: To assess microbiological, immunological, genetic, clinical, cognitive-behavioral, and epidemiological determinants for development of persisting symptoms in both adult and juvenile Lyme patients, and establish prediction rules * for the occurrence and intensity of persisting symptoms * for individual patients.
Secondary objective(s):
1- To assess the outcome and long-term effects of early localized, early disseminated and late disseminated Lyme borreliosis, both in children and in adults.
2- To assess what determinants of persisting symptoms in confirmed patients are existent in unconfirmed patients with existing persisting symptoms, and thus suggestive of similar mechanisms leading to persistence of symptoms, both in children and in adults.
3- To propose more personalized treatment and diagnostic strategies for both adult and juvenile Lyme borreliosis patients, which can be validated in further studies to asses to what extent they actually prevent and resolve long-term persisting symptoms in children and in adults.

Study design

This is a prospective observational cohort study without intervention but with invasive measurements.
We will prospectively investigate the long-term effects of Lyme borreliosis by a one year follow-up of 2000 adult and 300 juvenile patients with early localized, early disseminated or late disseminated Lyme borreliosis. Patients will be included before or just after start of treatment. In addition we will also include 300 adult and 50 juvenile patients with suspected but unconfirmed Lyme disease that have already developed persisting symptoms.

Study burden and risks

Participation in the study has no direct benefits for the subject. There is the possibility for the treating physician to contact the investigators for assistance in the diagnosis and (further) treatment, if during or after the study symptoms develop or persist. Participation contributes to enhanced insight in the development of persisting symptoms of Lyme borreliosis, and thus to the possible improvement of the diagnosis and/or treatment of people suffering from Lyme disease in the future. The burden of participation consists of blood sampling, filling in questionnaires, and for some of the adult participants also taking skin biopsies and skin swabs. We also include minors, who constitute 20-30% of all Lyme patients. Their specific risk to develop persisting symptoms after treatment should be assessed, as well as possible determinants/mechanisms for development of such symptoms. Based on the study results, treatment strategies specific for minors and/or adults can be proposed, in order to prevent or resolve persisting Lyme-related symptoms. For all study participants, upon request by a patient*s GP or medical specialist,

the project team can support diagnosis of possible Lyme-related disease or symptoms, facilitated by the study measurements if applicable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria are partly dependent on the patient group and the route of inclusion.
Patients included through Tekenradar.nl:
- are 5 yrs and older.
(there are no age restrictions for patients included through clinical Lyme centers)
EM patients included through Tekenradar.nl:

- report an EM at Tekenradar.nl with a diameter larger than 5 cm and that has been present for less than 3 months;
- have a confirmed (typical or atypical) EM diagnosed by their GP;
- have not yet started treatment for the EM or started maximum 4 days earlier at the moment of inclusion;
Confirmed Lyme patients:
- have a confirmed diagnosis of early or late Lyme borreliosis;
- have not yet started treatment at the moment of inclusion, or, if included via Tekenradar.nl at most 4 days before inclusion, or, if included via Clinical Lyme Centers, at most 1 week before inclusion.
Unconfirmed Lyme patients included through the Clinical Lyme Centers:
- symptoms that are present at the time of inclusion and have persisted for more than 6 months, such as myalgia and arthralgia, neuralgia, concentration disorders and cognitive disturbances, with or without fatigue.
- have a history of an unconfirmed suspicion for Lyme disease based on a positive result of a non-recommended diagnostic test OR onset of disease symptoms (as described above) that have started within one month after a documented tick bite;
-have a negative serological test for Borrelia spp.

Exclusion criteria

Exclusion criteria are partly dependent on patient group and route of inclusion.
All patients (and/or their parents/guardians):
- are unable to give informed consent or do not have a thorough command of the Dutch language.
Confirmed Lyme patients included through Tekenradar.nl:
-started treatment more than 4 days before inclusion.
Confirmed Lyme patients included through the Clinical Lyme Centers:
- started treatment more than one week before inclusion.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-04-2015
Enrollment:	2650
Type:	Actual

Ethics review

Approved WMO Date:	11-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 27509
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL50227.094.14
OMON	NL-OMON27509

Study results

Date completed: 14-10-2021

Actual enrolment: 1318

Summary results
Trial is onging in other countries