Recurrent respiratory tract infections (RRTI) in the elderly: from phenotypic and immunological characterizaton to a mechanistic unravelling of a potential primary immunodeficiency (PID).

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune system disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON42241

Source
ToetsingOnline

Brief title
Recurrent respiratory tract infections (RRTI) in the elderly.

Condition

- Immune system disorders congenital
- Bacterial infectious disorders
- Respiratory tract infections

Synonym
humoral deficiency; antibody immune defect

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Baxter,European Society for Immunodeficiencies

Intervention

Keyword: Antibody Deficiency Syndrome, Elderly, Primary immunodeficiency, Recurrent respiratory tract infection

Outcome measures

Primary outcome

Innate Immunity

1. integrity of the NADPH-oxidase pathway in granulocytes using the DHR123

assay.

2. cytokine production (IL-1β, IL-10, IL-12p40, IL-18, TNF, IFN-α, IFN-γ and

IFN-β) in whole

blood stimulated with TLR ligands (+/- IFN-γ) using Bioplex assays (Luminex).

3. complement activation (classical, alternative and MBL pathways) by Sandwich

Elisa.

Analyses of B cell subsets and function:

1. baseline gammaglobulin levels and subgroup analysis.

2. total number and percentages of total B cells (CD19+), naïve B cells

(IgG-IgA-/CD27-), IgMmemory

B cells (IgG-IgA-/CD27+), switch memory B cells (IgG+IgA+CCD27+), transitional B

cells (CD21+) and B1a cells (IgM+CD20+CD27+CD43+CD5+/-) by 16-color FACS on

PBMCs.

NB: depending on abberant B cell subset:

a. gene-expression in subset of B cells using microarray techniques.

b. Somatic Hypermutation in B cells with the IGH somatic hypermutation assay.

c. surface expression of receptors for BAFF and APRIL (BAFF-R, BCMA, TACI),

B7/PD-L1 and

CD40 on B cells using flowcytometry, and B cell proliferation after stimulation

with BAFF and anti-human IgM.

d. antibody responses after stimulation of B cells with pneumococci of

serotypes 3 and 4 with

and without covalent binding to C3, in the presence of CD40L and IL-10 by ELISA.

3. quantity of KREC*s using real-time qPCR.

4. antibody responses to PnPs antigens after vaccination with 23-valent

Pneumovax by

multiplexed bead assay (Luminex), one month and one year after vaccination.

5. antibody responses to vaccination with conjugated Prevenar (subsequent to

Pneumovax23).

Analyses of T cell subsets and function:

1. numbers of various lymphocyte subsets, such as: naïve CD4+/CD8+ T cells

(CD45RA+),

memory CD4+/CD8+ T cells (CD45RO+), and effector T cells (CD8+CD28-). Within

the CD4+

population: Th1, Th2, Th17, FOXP3+T-regs (CD4+CD25+), by 16-color FACS.

2. T-cell proliferation in response to PHA, PMA/ionomycin, high dose anti-CD3

and heat killed

pneumococci/PnPs antigens.

3. quantity of TREC*s using real-time qPCR.

4. cytokine production (IL-6, TNF, IL-4, IL-10, IFN-γ, IL-12, IL-17 and IL-2)

by PBMC*s stimulated

with PHA, PMA/ionomycin, high dose anti-CD3 and heat killed pneumococci, using

Bioplex

assays (Luminex).

Secondary outcome

nvt

Study description

Background summary

Primary immunodeficiencies (PID) are generally associated with children and treated within the field of
paediatric specialists. We know fairly well when to start the diagnostic and treatment processes. We also know that immunity weakens with age, a process that was coined *immunosenescence*. In addition, there is an upregulation of inflammatory responses, so-called *inflammaging*. These two processes culminate into a higher incidence of infections in seniors. However, research has yet to account for the incidence of recurrent infections at advanced age, and in particular for the role of defects in host immune responses in these infections. In our academic medical center, we identified over a period of 4 years, 22 elderly patients (median age 57 years) with late-onset recurrent respiratory tract infections (RRTI) of whom 45% displayed a weak response to unconjugated pneumococcal polysaccharide (PnPs) antigens (Pneumovax23 vaccination). These patients had low antibody titers despite normal concentrations of total IgG. It appears that normal immunosenescence and inflammaging cannot account for these occurrences of RRTI, and that these mild and previously concealed defects in immune responses of an ageing individual may be categorized as PID.

We hypothesise:
1) that there are mild PID in elderly patients with RRTI.
2) that the loss of adequate responses to PnPs antigens in a large proportion of these elderly is either due to a B cell intrinsic problem or to a regression in T cell independent (TI) co-stimulation of B cells affecting antibody production.
3) that PID in RRTI patients with normal responses to Pneumovax23 is due to (an)other still unknown mechanism(s).

Study objective

The overall aim of the proposed project is to identify mild PID in elderly patients that distinguish patients with RRTI from individuals with a healthy ageing innate and adaptive immune system. In innate immunity, normal immunosenescence is characterized by, among others, the accumulation of neutrophils with impaired antimicrobial functions. In adaptive immunity, an individual*s decreased B-cell response is correlated with changes in function and proportion of his T-cell population. A typical, known example of a mild PID is Mannose Binding Lectin (MBL) deficiency. In our pilotstudy identifying patients with inadequate responses to PnPs antigens, an unexpected high percentage (40% vs 5% in the general population) exhibited complete MBL deficiency.
Goals
I. Describe clinical disorder in elderly patients with RRTI.
II. Assess immune responses within this clinical phenotypes, both innate and adaptive.
III. Determine T cell independent condition of B cells in patients with RRTI and inadequate responses to PnPs antigens.

Study design

To identify clinical phenotypes and perform immunological assays in search for PID in elderly RRTI patients, we will recruit patients from the outpatient clinic of our two academic centers (LUMC and Erasmus Medical Center). We aim to admit 30 patients each (total of 60 patients). We will assess the innate and adaptive function of the immune system in all of them and analyse factors that are in some cases known to decay with age. For control purposes, we will sample 60 gender- and age-matched seniors from the population register, excluding those with RRTI or known immunodeficiency. In addition, in collaboration with the department of Geriatrics of the LUMC, we will randomly select 10 very old (90+) healthy individuals who are genetically enriched for longevity from the Leiden Longevity study to serve as extreme controls in our immunological studies.
Furthermore, we will collect DNA from all patients for future genetic studies investigating the association between recurrent respiratory tract infections with genetic variations in genes encoding pattern recognition receptors, their

adapters and downstream signalling molecules that are involved in the recognition of common pathogens found in RRTI (e.g., TLR1-4/6-9, NOD1, MDA5, MYD88, TIRAP, TICAM1/2), or associated with CF and CVID (CFTR, CARD11, TACI and POU2AF1). . In the current setting, the number of cases required for the association of genetic differences with mild effect and disease is unrealistic. Informed consent will be obtained from all patients and controls.

We will use a health questionnaires to assess the frequency and course of RRTI and possibly other infections in the 60 patients. Furthermore we will acquire bloodsamples by vena punction and perform several immunologic tests.

Study burden and risks

The burden and risks associated with participation in this study are small, and related to the venapunction only. The group of patients as a whole will benefit from the outcome of the study as it will help their treating phycisians to identify those patients with recurrent respiratory tract infections due to a primary immunedeficiency who are in need of a more rigorious antibiotic regime or IVIG.

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

- > 45 years old
AND
- two or more documented invasive bacterial or viral sino-, and/or pulmonary infections over the previous year
- no RRTI in early adulthood, adolescence or childhood
AND/OR
- an atypical microbial aetiology, an atypical course of infection or a belated response or early relapse on antibiotic treatments

Exclusion criteria

- secundary immunodeficiency (for example HIV, immunesuppresiva, malignancy)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-05-2015

Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	04-05-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL52171.058.15