The role of persistent gastrointestinal viral infections in the development of enteropathy in children with Common Variable Immunodeficiency and secundary immunodeficiencies

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To describe the prevalence of enteropathogenic viruses in children with primary (CVID and CVID-like disease) and secundary immunodeficiencies and a potential relation between this prevalence and the development of auto-/allo-immune enteropathy.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal infections
Study type	Observational non invasive

Summary

ID

NL-OMON39272

Source
ToetsingOnline

Brief title
Chronic gastrointestinal viruses in immunocompromised children

Condition

- Gastrointestinal infections
- Immunodeficiency syndromes

Synonym
defective antibody production of unknown cause, primary immunodeficiency

Research involving
Human

Sponsors and support

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

Intervention

Keyword: auto-immunity, CVID, gastrointestinal, viruses

Outcome measures

Primary outcome

1. The prevalence of enteropathogenic virus infections in children and

adolescents with CVID(-like disease) and SCT patients

2. An association between viral excretion and auto-/allo-immune enteropathy

Secondary outcome

1. The prevalence of symptomatic and asymptomatic enteropathogenic viral

infections in CVID(-like disease)

2. If any viruses are found: to assess

a. Duration of infection

b. Specification of the pathogen

c. Association between pathogen and clinical findings of the patient

3. To explore the potential differences in prevalence between the pediatric

CVID population, 'CVID-like disease' population and healthy

children/adolescents.

Study description

Background summary

Common Variable Immunodeficiency (CVID) is an immunodeficiency of unknown cause

that is characterised by an impaired B lymphocyte function, leading to e.g. recurrent bacterial and viral gastrointestinal infections. It is known that patients with such humoral immunodeficiencies can excrete viruses for several years.
Additionally, a considerable subgroup of CVID and CVID-like patients suffers from dysregulation of immune responses, causing chronic inflammation and/or autoimmunity, such as auto-immune enteropathy. Recent clinical findings suggest that chronic enteropathogenic viral infections can play a role in the development of auto-immune enteropathy in CVID(-like disease).
These dysregulated immune responses are also recognized in children with secondary immunodeficiency after stem cell transplantation. It is well-known that these patients are at risk of developing an allo-immune enteropathy or enteral Graft versus Host Disease. The recent finding of an association between plasma human herpes virus 6 and the development of pulmonal GVHD, combined with our own pilot findings of a substantial prevalence of gastrointestinal viruses in the stools of SCT patients, led us to hypothesize that chronic carriership of gastrointestinal viruses is associated with allo-immune enteropathy in SCT patients.

Study objective

To describe the prevalence of enteropathogenic viruses in children with primary (CVID and CVID-like disease) and secundary immunodeficiencies and a potential relation between this prevalence and the development of auto-/allo-immune enteropathy.

Study design

Follow up study in CVID and CVID-like disease patients aged 4-18 years, SCT patients aged 0-17 years and a healthy control group, consisting of minimally two and maximally 5 times an assessment of gastrointestinal complaints (not for SCT patients and faecessampling (after 3-6-12 and 18/24 months, maximal duration 2 years). De faeces samples will be screened by real time RT-PCR for enteropathogenic viruses: adeno-, rota-, entero-, noro-, parecho-, astro- and sapovirus. In addition, calprotectin will be tested, which is a parameter of protein loss via the stool used regularly in patient care. PCR positivity will lead to recurrent sampling to assess chronicity of the infection, and this will be correlated to the gastrointestinal complaints. Data on the development of auto-immune enteropathy will be extracted from the medical files and correlated to the previously mentioned data.
The protocol for SCT patients is slightly different, as they do not have to fill out questionnaires and faeces sampling will already be performed weekly during their peri-SCT hospital admission. The only additional faecessampling that will take place in the research setting is at 12 and 24 weeks post-SCT.

Study burden and risks

There are no risks associatied with the participation in this study.
Additionally, the burden of participation is very low: only 30 minutes or less in two years, with no invasive procedures. On the other hand, there is no direct benefit for the patients either.

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

CVID: diagnosed according to the ESID criteria:
Normal to low numbers of B lymphocytes.
Impaired specific antibody production after immunisation (less than 4-fold titer increase after

polysaccharide vaccination)
Low (<-2SD) serum immunoglobulin titers.
CVID-like disease: patients who do not fulfill the ESID criteria for CVID, but suffer from a similar clinical picture: at least one of the serum immunoglobulin(subclasses) is decreased (<-2SD), or there is insufficient antibody synthesis after immunisation less than 4-fold titer increase after polysaccharide vaccination). Secondly, patients suffer from recurrent infections, for which they are or have been treated with immunoglobulin substitution therapy for at least 6 months.
Healthy children: age 4-18 years
SCT patients: children aged 0-17 who will receive a stem cell transplantation (SCT) at the Wilhelmina Children's Hospital in order to treat their underlying disease, e.g. hematological malignancy, inborn metabolic disease such as Hurler's disease.

Exclusion criteria

For all patient groups: a proven primary immunodeficiency other than CVID, e.g. X-linked agammaglobulinemia (XLA) or hyper-IgM syndrome (HIGM), or a strong suspicion of one of these diseases.
For the healthy controls and SCT patients: immune disease, pre-existent gastrointestinal tract disease (e.g. Morbus Crohn, celiac disease, ulcerative colitis)

Study design

Design

Study type:	Observational non 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):	18-04-2010
Enrollment:	155
Type:	Actual

Ethics review

Approved WMO Date:	12-05-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-03-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-02-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL25746.041.08