The role of genetic variations in type I Interferons related to respiratory tract infections in Down Syndrome children.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON32178

Source
ToetsingOnline

Brief title
The Down Syndrome-Interferon study

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Immune disorders NEC
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Down Syndrome, innate immunity

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Down Syndrome, Innate immunity, Interferons, Respiratory tract infections

Outcome measures

Primary outcome

The primary study parameter is to identify a difference in mRNA expression level of IFN and IFN related genes between 1: Down Syndrome children and a control group of healthy children (siblings) and 2:between different DS children.

Secondary outcome

The secondary study parameter is to identify a relationship between mRNA expression levels and current/past history of respiratory tract infections in 1. DS children compared to siblings and 2. between different DS children.

Study description

Background summary

Children with Down Syndrome (DS) have a higher susceptibility to recurrent and more severe upper and lower (or secondary) respiratory tract infections in comparison to children without DS, resulting in an increased frequency of hospitalization. Earlier research within our group shows preliminary evidence that DS children have a dysregulated IFN response following ex vivo stimulation with Influenza A virus. In this pilot project, we aim to study in more detail the mechanism of IFN dysregulation and to identify dysfunctional components of the Interferon signaling pathway in order to create a risk profile for disease, namely the higher susceptibility to respiratory tract infections in DS children. Identification of DS children who are at an increased risk for (severe) respiratory tract infections allows preventive measures to be taken. In the future, specific therapies may be developed which target the dysfunctional components of the immune response in these children.

Study objective

The main objective is to identify a difference in mRNA expression level of IFN and IFN related genes between Down Syndrome children and a control group of healthy children (siblings).
The secondary objective is to identify a relationship between mRNA expression levels and history (current/past) of respiratory tract infections.

Study design

Observational study

Total duration: 6 months-1 year

Setting: outpatient clinic and laboratory

Study procedures:
A. Patient-related: single visit to the outpatient clinic:
1. Interview with participants or parents of participants regarding history of respiratory tract infections (see attachment).
2. Blood collection from each participant: Total volume: 7,5 ml (2,5 ml collected in PaxGene tube for baseline mRNA expression measurements, 4 ml heparinized blood for full blood stimulation experiments, 1 ml of blood for analysis of C-Reactive protein level, complete blood count, and leukocyte differentiation).

B. Laboratory-related:
Laboratory of Clinical Chemistry VUmc: laboratory analysis of infection parameters (C-Reactive protein level, complete blood count, and leukocyte differentiation).

CCA/V-ICI laboratory VUmc:
In the blood samples, we will measure gene expression of several genes of interest, measured by mRNA expression levels using Real Time PCR. Gene expression will be measured at baseline and following in vitro stimulation of whole blood with five different ligands (see protocol).

Ligands:
Interferon alpha, single stranded RNA (ssRNA), Lipopolysaccharide (LPS), CpG DNA and Poly I:C.

Genes of interest:
1. IFN type I and II genes: IFN alpha, -beta and *gamma
2. IFN response genes: MxA, RSAD2, ISG15, IRF5

3. IFN alpha and gamma receptor subunits: IFNAR1, IFNAR2, IFNGR1, IFNGR2
4. TLR genes: TLR 3, 4, 7, 9

Study burden and risks

The burden involves a single visit to the outpatient clinic, an interview regarding the history of respiratory tract infections, and venapuncture. The venapuncture can cause pain, discomfort, or a hematoma at the site of the venapuncture.
The risks are similar to the risks of a venapuncture performed for other reasons.

We specifically want to include a group of Down syndrome children because this group has an even higher susceptibility to respiratory tract infections compared to children without Down syndrome. Preliminary results point to a dysregulation in the Interferon system, and we therefore want to explore whether a dysregulated Interferon system is correlated to a higher susceptibility to respiratory tract infections. The information and results obtained from this study may contribute to predicting which Down Syndrome children have a higher risk of severe respiratory tract infections and to the development of specific measures and/or therapies for this high risk group.

We want to include the siblings of these Down syndrome children because they share a common genetic background and a similar environmental exposure to pathogens, except that they do not have a chromosomal abnormality. This allows us to compare two groups with shared common variables and differing only in the number of copies of chromosome 21.

Participants will not have a direct benefit from this study. We believe that the possible benefits from information obtained from this study regarding the immune response in Down syndrome children outweigh the inconvenience of participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Written informed consent from both parents or legal guardian (s).
2. Age 2 until and including 17 years
3. Sex: male and female
4. Ethnic background: Caucasaian and Non-Caucasian
5. Down Syndrome: Trisomy 21 due to meiotic non-dysjunction
6. Siblings: healthy, no known diseases

Exclusion criteria

1. Not meeting inclusion criteria
2. Clinically ill (infection) at time of venapuncture
3. Down Syndrome: Trisomy 21 due to mitotic non-dysjunction or mosaicism.
4. Siblings: with known congenital, syndromal or immunological disorders or other known diseases

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):	01-08-2008
Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO

Date:	19-08-2008
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL22885.029.08