Does a deregulated PI3K/Akt-pathway affect the immune system in children with Down syndrome?

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1. To examine whether the PI3K-AKT pathway is overly activated in children with Down syndrome compared to healthy age-matched controls. 2. To determine the rate of exhaustion and the apoptosis of lymphocytes in children with DS. 3. To determine the...

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

Summary

ID

NL-OMON46498

Source
ToetsingOnline

Brief title
Akt-signalling in Down syndrome

Condition

- Immune disorders NEC

Synonym
Activated PI3K/Akt-pathway, immunophenotype

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis
Source(s) of monetary or material Support: Salaris van de (lokale) instelling voor de onderzoeksmedewerkers. Daarnaast zal financiering uit lokale fondswerving worden

aangevraagd.

Intervention

Keyword: AKT-pathway, Children, Down syndrome, immunology

Outcome measures

Primary outcome

Deregulated AKT phosphorylation assays in both groups.

Secondary outcome

B- and T-cell subset abnormalities, rate of apoptosis, exhaustion present in

lymphocytes and immunoglobulines.

Study description

Background summary

Down syndrome (DS) is associated with a higher prevalence of auto-immune diseases and infections. Moreover, severe respiratory tract infections are one of the major causes of death in individuals with DS. Detailed knowledge of the impaired immune system in DS and its contribution to the susceptibility to infections is scarce. Patients with activated PI3K-* syndrome (APDS) have an immunological phenotype and clinical presentation resembling to patients with DS. The mechanism responsible for APDS is the over-activation of the PI3K-AKT-pathway, which was also activated in one of our own patients with DS. Also, research comparing healthy adults with individuals with DS showed hyperactivation of this pathway in the frontal cortex in DS. Therefore, we hypothesize that the altered immune system of children with DS can be partially explained by an increased activity of the PI3K-AKT pathway, enhancing the risk to suffer from infections such as severe respiratory tract infections (RTIs).

Study objective

1. To examine whether the PI3K-AKT pathway is overly activated in children with Down syndrome compared to healthy age-matched controls. 2. To determine the rate of exhaustion and the apoptosis of lymphocytes in children with DS. 3. To determine the association between the AKT-pathway and the degree of antibody deficiency and clinical symptoms in children with DS.

Study design

Observational non-interventional cohort study with a cross-sectional design comparing the immunological characteristics of children with DS with healthy age matched children (n=42). The study results will be compared to data from APDS patients as a model of proven PI3K-AKT over-activation.

Study burden and risks

Clinical data will be collected during regular clinical follow up visits. The (extra) blood sample will be collected when blood gets drawn for regular healthcare purposes. In the control group, samples will be collected from the peripheral intravenous catheter which is placed for clinical reasons (minor surgery). There is no extra risk for the child because it will not result in an extra intervention. Only minors will be included in the study, as the onset of infections is predominantly present in childhood. This study does not directly benefit patients with Down syndrome and healthy controls. If our hypothesis proves to be correct the AKT-pathway eventually might serve as a therapeutic target to reduce morbidity and mortality among patients with Down syndrome.

Contacts

Public
HagaZiekenhuis

Els Borst-Eilersplein 275
Den Haag 2545 AA
NL
Scientific
HagaZiekenhuis

Els Borst-Eilersplein 275
Den Haag 2545 AA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age 1 month-18 years;
- For subjects with Down syndrome: diagnosis by chromosomal analysis;
- For healthy age-matched controls: undergoing a minor surgical procedure;
- Weight >5 kg;
- Informed consent from parent(s)/caregiver(s) with legal custody and/or the subject (according to the WGBO).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Any active infectious disease (viral or bacterial), excluding mild upper respiratory tract infections without fever;
- Any type of malignancies, including lymphoproliferative disease (except of squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence);
- Mosaic Down Syndrome;
- Current treatment with prophylactic antibiotics, monoclonal antibodies or immunosuppressant*s;
- Auto-immune diseases other than those associated with Down Syndrome;
- For healthy individuals: known with recurrent respiratory tract infections (RRTIs) and/or getting ear, nose or throat (ENT) surgery because of this reason.

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2018
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO Date:	06-03-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-05-2019
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	NL63464.098.17