Genetic Risk factors for Multi-system Inflammatory Syndrome in Children and Pediatric Post COVID condition (GRIP)

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Primary objective: To identify rare, high impact genetic variants in immunological genes and pathways in children with a history of MIS-C or pediatric post-COVID condition. Secondary objectives: To analyze the clinical characteristics and long-term...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Observational non invasive

Summary

ID

NL-OMON53446

Source
ToetsingOnline

Brief title
GRIP

Condition

- Immunodeficiency syndromes

Synonym
MIS-C and Post-COVID

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Genetic, MIS-C, Pediatric, Post-Covid

Outcome measures

Primary outcome

- Individual analysis of immunological genes in cases only: We will restrict our analysis to pathogenic (class 5) or likely pathogenic (class 4) variants in genes known to be associated with monogenic inborn errors of immunity to diagnose previously unsuspected inborn errors of immunity (IEI) in MIS-C or post-COVID condition cases.

- Case-control study: We will evaluate if a larger proportion of cases with MIS-C or post-COVID condition have rare and presumably deleterious variants in immunological genes than children with an asymptomatic or mild infection.

Secondary outcome

We will evaluate if genetic variants correlate with clinical parameters, such as severity of illness and response to treatment.

Study description

Background summary

Following infection with SARS-CoV-2, some children develop the potentially life-threatening disease Multi-System Inflammatory Syndrome in Children (MIS-C) and some children develop post-COVID condition (formerly *long COVID*). It is unknown why some children develop severe or prolonged symptoms after SARS-CoV-2 infection, while most children have asymptomatic or mild disease. We hypothesize that rare variants in genes associated with the immune system predispose children to develop MIS-C or post-COVID condition after infection with SARS-CoV-2.

Study objective

Primary objective: To identify rare, high impact genetic variants in immunological genes and pathways in children with a history of MIS-C or pediatric post-COVID condition.
Secondary objectives: To analyze the clinical characteristics and long-term effects of pediatric COVID-19 and MIS-C. To characterize the functional and clinical impact of genetic variants in MIS-C and post-COVID condition and identify targets for therapy.

Study design

We will do an observational study. We will perform Whole Exome Sequencing (WES) using Next Generation Sequencing (NGS) on DNA from blood or saliva. We will include: (1) MIS-C cases: Children with a history of MIS-C; (2) post-COVID condition cases: Children with post-COVID condition; and (3) Controls: SARS-CoV-2 exposed age-matched control group: children who were infected with SARS-CoV-2 but did not develop moderate to severe COVID-19, MIS-C or post-COVID condition. We will do immunological analyses to validate the results of the genetic study. We will evaluate if certain genetic risk factors aggregate in specific subgroups of patients.

Study burden and risks

Results of this study are related to the target group (i.e. children with SARS-CoV-2 infection). Children with MIS-C or post-COVID condition participating in this study may benefit directly, if an immunological condition is identified that warrants treatment or follow-up. Controls will not directly benefit from this study, since genetic data from the controls is analyzed at *group level* in the case-control study. To minimize burden we will send participants a saliva DNA home collection kit. These can be returned by regular mail. Samples for the immunological studies have already been collected and stored. We may request for one additional blood sample if the stored material is insufficient in quality or quantity and we need to validate the functional impact of a genetic variant. If this is needed, this will only be done after additional informed consent.

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)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Children with a history of MIS-C: as defined according to WHO criteria [36], who were 0-18 at the time of MIS-C
2. Children with post-COVID condition who were 0-18 at the time of SARS-CoV-2 infection: as defined according to the WHO case definition [37].
This includes a history of probable or confirmed prior SARS-CoV-2 infection, with signs and symptoms (including fatigue, shortness of breath, cognitive dysfunction) that are present after 12 weeks, last at least 2 months, have an impact on daily functioning and are not explained by an alternative diagnosis. Post-COVID condition must be diagnosed by a pediatrician.

3. *Exposed* control group: children with a history of proven SARS-CoV-2 infection (RT-PCR, antigen test or serology positive) who were 0-18 at the time of SARS-CoV-2 infection.

Exclusion criteria

1. Group 1 (MIS-C): no specific exclusion criteria
2. Group 2 (post-COVID condition): other plausible cause of symptoms AND/OR a history compatible with chronic fatigue syndrome prior to infection with

SARS-CoV-2. Children with a history of MIS-C who suffer prolonged signs and symptoms will be included in the MIS-C group. Patients who were not diagnosed with Post-COVID condition by a pediatrician, but only by for example a general practitioner, are excluded.
3. Group 3 (*exposed* control group): MIS-C or post-COVID condition; AND/OR Moderate or severe course of COVID-19, defined as: need for supplemental oxygen and/or intensive care admission because of COVID-19 and/or death. Children are also excluded when they have had a vaccination against SARS-CoV-2, before their first infection with this virus. Also, the children in de the exposed control group are excluded when their parents/siblings (1st degree family) suffer(-ed) from MIS-C or post-COVID condition.

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:	Recruiting
Start date (anticipated):	07-10-2022
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO

Date:	28-06-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-10-2023
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	NL80853.058.22