TET2 Expression in Pediatric Pulmonary Arterial Hypertension

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Ethical review	Approved WMO
Status	Pending
Health condition type	Pulmonary vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON57396

Source
ToetsingOnline

Brief title
TET2-PAH

Condition

- Pulmonary vascular disorders
- Vascular hypertensive disorders

Synonym
high blood pressure in the lungs, Pulmonary Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Stichting Vrienden Beatrix Kinderziekenhuis

Intervention

Keyword: Biomarker, Inflammation, PAH, TET2 expression

Outcome measures

Primary outcome

The primary objective is to determine whether TET2 mRNA expression in peripheral blood mononuclear cells (PBMCs) is reduced and serum levels of IL-1β and IL-18 are elevated in pediatric PAH patients when compared to age- and sex-matched controls.

Secondary outcome

- Investigate whether TET2 expression in PBMCs associates with disease severity markers used in the clinic during standard follow-up in pediatric PAH patients. Currently, the clinical markers used during standard follow-up include:

- Serum N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), a marker for right ventricular dilatation

- WHO functional class, a 4-point scale where all patients are assigned a severity class by the physician

- Tricuspid Annular Plane Systolic Excursion (TAPSE), which is measured by echocardiography and is considered the gold standard for assessment of right ventricular function

- Investigate whether the serum level of IL-1β associates with NT-pro-BNP, WHO functional class, and TAPSE in patients with pediatric PAH.

- Investigate whether the serum level of IL-18 associates with NT-pro-BNP, WHO functional class, and TAPSE in patients with pediatric PAH.

- Investigate whether serum IL-1β and IL-18 levels inversely correlate with the

TET2 expression in PBMCs in patients with pediatric PAH.

Study description

Background summary

Pulmonary arterial hypertension (PAH) is a rare severe pulmonary arteriopathy with poor survival due to development of right-sided heart failure. PAH can occur in children (pediatric PAH) and adults. When PAH is diagnosed, pulmonary vasodilators that are used as a therapy, improve survival, but the disease cannot be cured, leaving heart and lung transplantation as the ultimate treatment option. We thus need additional therapies for PAH.
PAH is an inflammatory vasculopathy. A master-regulator of inflammation is interleukin (IL)-1β. The secretion of IL-1β, and also IL-18, is controlled by inflammasomes. While serum IL-1β and IL-18 are elevated in adult PAH patients, suggestive of inflammasome activation, it is unclear whether the inflammasome is activated in pediatric PAH. Our findings in a rat model of pediatric PAH have shown that specifically the NLRP3 inflammasome is activated during PAH and that its inhibition ameliorates pediatric PAH. We now ask whether the NLRP3 inflammasome is activated in pediatric PAH and may be a therapeutic target; and at the same time we aim to identify biomarkers for inflammasome activation in pediatric PAH. Recent studies in adult PAH have suggested that low expression of ten eleven translocation 2 (TET2) in peripheral blood mononuclear cells (PBMCs) may be a biomarker for inflammation-associated PAH. We now aim to define whether this is also the case in pediatric PAH.

Study objective

We aim to identify if pediatric PAH patients have increased plasma IL-1β and IL-18 compared to control participants, as well as increased caspase-1 cleavage and NLRP3, IL-1β and IL-18 mRNA expression in PBMCs, reflective of inflammasome activation. We also aim to compare TET2 mRNA expression in PBMCs between the pediatric PAH group and the control group in order to interrogate its potential as biomarker for inflammation-associated pediatric PAH.
We hypothesize that PAH patients show increased serum concentrations of IL-1β, IL-18, as well as increased caspase-1 cleavage and NLRP3, IL-1β, and IL-18 mRNA expression and decreased mRNA expression of TET2 in PBMCs.

Study design

The current study is a single-center, cross-sectional, case-control observational study. The study population consists of PAH patients and control individuals who will be children seen at the outpatient clinic of the Beatrix Children*s Hospital. We will obtain blood from PAH patients and control

patients during an already planned venipuncture at an outpatient visit or as part of a pre-operative blood work-up for hospital admission. From each participant, we will collect 15 ml of blood for monocyte and serum isolation. 10 ml will be withdrawn for monocyte isolation, and another 5 ml will be collected for serum analysis during a venipuncture already performed as part of their routine clinical care. Processing and storage of the samples will occur in the Laboratory of Pediatrics in the UMCG.

The control group consists of patients seen at the outpatient clinic of the Beatrix Children*s Hospital. These patients already undergo venipuncture during an outpatient visit or during pre-operative blood work-up as part of standard care. Control participants are recruited from the departments of general pediatrics, endocrinology, nephrology, and gastroenterology. Inclusion criteria for control participants involve the absence of a diagnosis related to pulmonary vascular disease, heart failure, an infection, inflammation or an immunological comorbidity. All participants with an acute infection or inflammatory condition with fever (determined through anamnesis) during the last week before the blood collection, or other systemic symptoms on the day of blood collection, will be excluded. After blood collection, participants with a serum of CRP >10 mg/L or monocytes >10% of white blood cell count will be excluded.

Study burden and risks

This study has important potential benefits for the pediatric PAH population. The identification of the IL-1β and IL-18, being the main products of inflammasome activation, in the serum of the patients has not been reported in the pediatric population. Validating our preclinical findings in a pediatric patient population would reinforce our understanding of the role of inflammation in the pathophysiology of this disease. Understanding the mechanisms through which PAH progresses allows for identification of potential therapeutic targets in the future.
Furthermore, describing the role of inflammation in PAH can also result in better clinical monitoring of the disease. As mentioned before, current monitoring tools have major limitations in the pediatric population and only reflect mechanical strain. A biomarker reflecting pathophysiological disease progression directly, obtained in a minimally invasive way could allow us to monitor the disease by processes connected to the vascular remodeling of the pulmonary vasculature compared to the current biomarkers reflecting the right sided heart failure. Decreased TET2 expression is upstream of NLRP3 activation, and as such could be used to track inflammation and disease progression.

Regarding the risks, venipuncture has low physical risk, including redness, bleeding and infection. Venipuncture may cause discomfort and even traumatize pediatric patients who have a history of extensive hospital admissions. To minimize the burden, we collect blood samples during an already planned venipuncture as part of standard care. The amount of blood that will be

withdrawn is negligible (15 ml), even in children. The venipuncture is performed by specialized personnel. We thus believe that our study adds minimal burden to the subjects.

Our pediatric PAH cohort also consists of children that have conditions that impair their decision-making (at least 15% of our cohort) and these children are therefore not legally competent to make their own decisions. Considering that these patients already undergo venipuncture for standard care, we consider the additional burden of participation of these individuals minimal.

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

PAH group:
1. PAH diagnosis, confirmed by right heart catheterization
2. aged 2 to 18 years
3. informed consent depending on the age, by the child and/or the legal guardian/parent.

Control group:
1. No diagnosis of PAH, (signs of) heart failure, conditions of pulmonary vascular disease or conditions associated with pulmonary vascular remodeling, cardiac arrythmia, cardiomyopathy, congenital heart disease, infection, inflammation or immunological comorbidities.
2. aged 2 to 18 years
3. informed consent depending on the age and competency, by the child and/or the legal guardian/parent.

Exclusion criteria

A potential subject either from the control or the PAH group who meets any of the following criteria will be excluded from participation in this study:
1. a medical history of immunologic or chronic inflammatory conditions
2. signs/symptoms of an active infection within 1 week prior to blood withdrawal, indicated by anamnesis and/or CRP >10 mg/L or monocytes >10% of white blood cell count.

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:	Pending
Start date (anticipated):	01-03-2025
Enrollment:	90
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	18-03-2025
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL87754.042.24