The role of glucocorticoid receptor sensitivity in congenital adrenal hyperplasia

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Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON57466

Source
ToetsingOnline

Brief title
CAHsense

Condition

- Endocrine disorders congenital
- Adrenal gland disorders

Synonym
Congenital adrenal hyperplasia, inherited adrenal disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Dioraphte

Intervention

Keyword: Congenital Adrenal Hyperplasia, Glucocorticoid receptor, Mononuclear Leukocytes

Outcome measures

Primary outcome

The main study parameters are the inhibition of lipopolysaccharide

(LPS)-induced cytokine production in peripheral blood mononuclear cells

(PBMCs) after ex vivo glucocorticoid exposure (measure of GRS) and the

expression of genes indicative of GRA, such as FKBP5.

Secondary outcome

Secondary outcomes will comprise serum/saliva cortisol, PS, and AA levels and

clinical outcomes.

Study description

Background summary

Congenital adrenal hyperplasia (CAH) is a group of rare autosomal recessive disorders characterized by enzymatic deficiencies in adrenal steroidogenesis, primarily due to 21-hydroxylase deficiency, affecting approximately 1 in 15,000 individuals. This enzymatic defect results in impaired cortisol synthesis and the accumulation of precursors steroids (PS) and adrenal androgens (AA). Lifelong glucocorticoid replacement therapy is required to manage cortisol insufficiency, and patients must adjust their cortisol dosage during stress to prevent life-threatening adrenal crises. Over- or undertreatment can lead to long-term complications: undertreatment may result in infertility, cardiovascular disease, and metabolic disorders, while overtreatment can cause obesity, hypertension, and other metabolic symptoms. The cortisol dosage required to normalize AA levels is often supraphysiological and varies widely between individuals, which we hypothesize is due to interindividual variability in glucocorticoid receptor sensitivity (GRS) and the modulatory effects of elevated PS on glucocorticoid receptor activity (GRA). Comparing this variability with patients with Cushing*s syndrome, who experience excess cortisol and likely altered GRS, and healthy volunteers could provide important insights. A better understanding of these factors could lead to more

personalized and optimized therapeutic strategies, reducing the risks of both over- and undertreatment in patients with CAH.

Study objective

The aim of this study is to investigate the GRS in CAH patients and compare these findings with patients with Cushing's syndrome and healthy controls. Additionally, this study will examine the influence of PS and AA on GRA to better understand the variability in treatment response in CAH.

Study design

an explorative cross-sectional study using an ex vivo PBMC mode

Study burden and risks

For patients and healthy volunteers, there is no direct benefit in participating in this study. However, by participating, they can contribute to the acquisition of scientific knowledge and the development of biomarkers to predict response to treatment and prevent complications due to over- or undertreatment. The risks associated with this study are negligible, as no additional interventions beyond routine patient care will be performed. Blood will be collected when a venipuncture is already scheduled. Therefore, this study is considered to impose a low burden on patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

For all groups:
• Aged >= 16 years
• Capable of providing informed consent

Inclusion criteria for patients with CAH:
• Diagnosed with classical CAH

Inclusion criteria for patients with Cushing*s syndrome
• Diagnosed with Cushing*s syndrome
• Not currently receiving any form of treatment for Cushing's syndrome (e.g., no surgical interventions aimed at reducing cortisol production)

Exclusion criteria

• Unable to provide informed consent
• Pregnancy
• Use of systemic glucocorticoids for medical indications other than the treatment of
CAH within the past 3 months.
• Active inflammatory or infectious comorbidities
• Acute illness or infection in the past 2 weeks

Study design

Design

Study type: Observational invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2025
Enrollment:	80
Type:	Anticipated

Ethics review

Approved WMO

Date:	12-05-2025
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL88865.091.25