Cardiovascular risk profile in pediatric CAH patients: a cross-sectional study

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Ethical review	Approved WMO
Status	Pending
Health condition type	Adrenal gland disorders
Study type	Observational non invasive

Summary

ID

NL-OMON38496

Source
ToetsingOnline

Brief title
Cardiovascular risk in CAH

Condition

- Adrenal gland disorders

Synonym
Congenital aderenal hyperplasia;

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: NWO AGIKO subsidue

Intervention

Keyword: Cardiovascular risk, Congenital adrenal hyperplasia, Glucocorticoids

Outcome measures

Primary outcome

Comparisson of the different cardiovascular riskfactors between CAH patients

and reference values.

- Insulin resistance

- left ventricular hypertrophy

- intima media thickness

- body composition

- 24-h systolic and diastolic bloodpressure

- 24-h urinary steroid profile

- circulating biochemical risk markers (e.g. lipids)

Secondary outcome

-

Study description

Background summary

Congenital adrenal hyperplasia (CAH) is a disorder of adrenal steroidogenesis. In 95% of cases it is caused by 21-hydroxylase deficiency.1 Deficiency of 21-hydroxylase results in impaired adrenal synthesis of cortisol and often also of aldosterone leading to increased secretion of ACTH, adrenal hyperplasia and excessive production of adrenal precursors before the enzymatic bloc such as 17 hydroxyprogesterone. The production of adrenal androgens is not disturbed. Therefore, adrenal hyperplasia will lead to excessive production of adrenal androgens. Treatment with glucocorticoids and, if necessary, mineralocorticoids prevents adrenal crises and suppresses abnormal secretion of adrenal androgens. Usually supraphysiological doses of glucocorticoids are needed to suppress

androgen levels. In the case of illness the glucocorticoid dosage even has to be increased.
Patients with CAH, who are treated with supraphysiological doses of glucocorticoids, are at risk of developing signs and symptoms of Cushing*s syndrome. As hypercortisolism is associated with hypertension, obesity with abdominal fat accumulation and diabetes mellitus, it is not unlikely that patients with CAH may show an adverse cardiovascular and metabolic risk profile, possibly leading to a reduced life expectancy. Furthermore, mineralocorticoid excess may play a role in the development of high blood pressure. Only recently, we systematically reviewed all the available data on body mass index (BMI), body composition, blood pressure, insulin sensitivity and lipid profiles in adult and pediatric CAH patients. Indeed, the literature suggests that adult CAH patients seem to have a high risk to cluster a number of risk factors, resembling the criteria of the metabolic syndrome. Several studies have been performed evaluating cardiovascular risk factors in both adult and pediatric CAH patients. Some of these studies were performed within our study group. These studies show that adult CAH patients are characterized by an elevated BMI, a changed body composition (towards an increased fat mass and more abdominal fat), insulin resistance, and elevated blood pressure levels.5 Furthermore, an increased intima-media thickness (IMT) was described in adult CAH patients. An increased IMT has been described as a surrogate marker of atherosclerosis and consequently a higher cardiovascular risk. Data on cardiovascular risk factors in pediatric CAH patients is scarce. During childhood, a tendency towards high blood pressure and elevated BMI have been shown. One study showed pediatric CAH patients (both caused by 21-hydroxylase deficiency and other deficiencies) to be insulin resistant. Unfavorable changes in the cardiovascular risk profile may be due to both effects of treatment (glucocorticoids, mineralocorticoids) and high androgen levels. No systematic research on cardiovascular risk factors has been performed in pediatric CAH patients. Because several of the risk factors were found abnormal in adult patients, evaluation in childhood is essential.

Study objective

We hypothesize that cardiovascular risk factors may already be present during childhood in CAH patients. Therefore, we will perform a cross-sectional study in CAH patients aged 1-16 years evaluating blood pressure, lipid profile, insulin sensitivity, cardiac function (electrocardiography (ECG), echocardiography), IMT, body composition (Dual Energy Xray Absorptiometry (DEXA) scan), and several biochemical cardiovascular risk markers. Furthermore, we want to incorporate recently developed and well-established echocardiography techniques (Tissue Doppler, strain en strain rate imaging) to identify early signs of myocardial dysfunction.

Study design

Patients and methods and data collection
Patients
All CAH patients, due to 21-hydroxylase deficiency, with biochemical and genetically proven CAH, aged 0-16 years treated within the Radboud University Nijmegen Medical Centre (n=80) will be included in this study. Baseline characteristics (date of birth, mutation analysis, target height (SDS), current height (SDS), hydrocortisone and fludrocortisones dose, bone age) will be collected for all patients from their individual electronic patients medical file.
Exclusion criteria will be:
• Inability to give written consent for the study.
• Known co-morbidity: cardiac disease, renal disease, co-medication that interferes with blood pressure.
Methods
Written informed consent will be asked to both parents and children above 12 years old.
Each participant will visit the hospital on two consecutive days that will be combined with a regular visit to the outpatient clinic. On the first day, participants will visit the hospital at 8.30 a.m. after an overnight fast.
Before taking morning medication a maximum of 38 ml blood (in neonates a minimum of 2.5 ml and a maximum of 21 ml) will be taken to assess the following biochemical markers: fasting glucose, HbA1C, insulin, lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), plasma catecholamines and metanephrines, aldosterone, renin, ACTH, leptin, adiponectin , hsCRP, IL-6, IL-18, TPA, PAI-1. Insulin resistance (IR) will be estimated using the homeostasis model assessment (HOMA) method [IR = insulin (µmol/ml) x glucose (mmol/l)/22.5]. Residual blood will be stored anonymised for future research.
Afterwards all participants will have a routine visit scheduled to their treating pediatric endocrinologist in our outpatient clinic. The participants receive a physical examination including anthropometric measurements and hip and waist circumference. Subsequently, blood pressure will be assessed under real-life conditions using 24 hours ambulatory blood pressure monitoring (24h-ABPM) in patients older than 5 years. During 24 hours blood pressure measurements patients and their parents will register physical activities and time of going to sleep and waking up in a diary. Furthermore, the patients will receive a container to collect all urine during 24 hours. A urinary steroid profile will be analyzed to be informed about hormonal control in the treated CAH patients and to measure other steroids and adrenal metabolites that might be elevated in CAH patients. On the second day, participants will return to the hospital for disconnection of the ambulatory blood pressure monitoring device and to return the collected urine. Echocardiography, including recently developed techniques (Tissue Doppler, strain en strain rate imaging) will be performed according to a strict protocol by an experienced echo technician and supervised by one experienced pediatric cardiologist (LK) to evaluate cardiac function with left ventricular hypertrophy as main outcome measure. IMT measurement will be performed attached to the echocardiography protocol in

order to determine the level of atherosclerosis. Additionally an ECG will be performed. A DEXA scan will be performed to evaluate body composition in patients older than 12 years. A DEXA total-body scanner will be used to obtain regional and whole body composition measurements using a three-compartment model of body composition: lean tissue mass (LTM), fat tissue mass (FTM), and bone mineral content (BMC). LTM, FTM and BMC will be determined using software algorithms based on derived regression equations. Percentage of body fat by DEXA for total body will be calculated using the formula:100•FTM/ (FTM + LTM + BMC). Scanning time will be approximately 20 to 30 minutes.
Collected data will be compared to internationally accepted reference values for the different cardiovascular risk markers therefore a control group is not necessary.

Study burden and risks

Hospital visits on 2 consecutive days for several non-invase diagnostic tests.
24-h bloodpressure measurement.
DEXA total body scan.
Blood test.

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

CAH due to 21-hydroxylase deficiency, biochemical and genetically proven
Age: 1-16 years

Exclusion criteria

CAH due to other enzym deficiency
Refusal to participate by patient/parents
Known co-morbidity: cardiac disease, renal disease, co-medication that interferes with blood pressure

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2013
Enrollment:	80
Type:	Anticipated

Ethics review

Approved WMO Date:	13-11-2013
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	NL44577.091.13