Blood pressure and steroid metabolism in the first year of life in patients with congenital adrenal hyperplasia (CAH): a longitudinal study

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To evaluate the blood pressure within the first year of life we will perform a prospective longitudinal study in all newborn patients with the classical form of CAH. To analyze the urinary steroid profile in CAH patients and healthy controls during...

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

Summary

ID

NL-OMON34023

Source
ToetsingOnline

Brief title
Blood pressure and steroid metabolites in the first year of life in CAH

Condition

- Endocrine disorders congenital

Synonym
Congenital adrenal hyperplasia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: ZonMw subsidie

Intervention

Keyword: Congenital Adrenal Hyperplasia, Glucocorticoids, Hypertension, Mineralocorticoids

Outcome measures

Primary outcome

1. Blood pressure profiles during the first year of life in CAH patients.

2. Urinary steroid profiles in healthy neonates and newborn CAH patients.

Secondary outcome

None

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. 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. In most studies in older children with CAH a tendency towards high blood pressure was shown. Blood pressure has not been studied in CAH patients within the first year of life. Our pilot study showed that within the first

weeks of life blood pressure is not significantly elevated in the first year of life. However, evaluation of the first week of life was not performed.
Not only medical treatment but also elevated concentrations of adrenal androgens and other elevated steroid metabolites may cause an unfavorable cardiovascular risk in CAH patients. It has been reported that in healthy full-term newborn Japanese neonates the levels of adrenal 16 alpha-, 16 beta-, and 15 beta-hydroxy metabolites of 3 beta-hydroxy-5-en-steroids, and 6 beta-, 18-hydroxy and 11-oxo-metabolites of corticosteroids are significantly higher than in healthy adults. In Caucasian healthy neonates and in CAH patients the full spectrum of adrenal steroids has not been studied with currently available very sensitive and specific techniques.

Study objective

To evaluate the blood pressure within the first year of life we will perform a prospective longitudinal study in all newborn patients with the classical form of CAH.
To analyze the urinary steroid profile in CAH patients and healthy controls during the first weeks of life.

Study design

Blood pressure measurements

Newborn female CAH patients are usually hospitalized in our centre due to ambiguous genitalia. Male newborn CAH patients will be usually hospitalized in our center after presentation with a positive neonatal CAH screening. All blood pressure measurements will be performed using an appropriate sized cuff on the Dinamap Vital Signs Monitor (GE Healthcare, Finland). Before and after initiation of treatment with hydrocortisone and fludrocortisone blood pressure will be measured at a three hour time interval during 24-hours to evaluate the direct effect of fludrocortisone and hydrocortisone on the blood pressure, as ambulatory 24-hour blood pressure measurement devices are not applicable for neonates.
During every visit to our outpatient clinic (that routinely takes place every one to two weeks within the first two months and thereafter every 6 weeks) blood pressure will be measured before taking the medication (08.30 a.m.). An experienced nurse will measure all blood pressures with the parents calming the patients, for example by feeding the child. When the child cannot be calmed the blood pressure will be measured again at the end of the clinical visit when the infant is calmed or sleeping. Thereafter, blood samples will be collected and physical examination will take place according to our current follow up protocol. Hydrocortisone replacement consists of 1 mg hydrocortisone thrice-daily during the first eight months of life. The fludrocortisone dose will be adjusted to serum renin levels and if blood pressure is above the 90th percentile for age and sex.

This study will be performed within the Radboud University Nijmegen Medical Center, department of pediatric endocrinology. No additional blood samples have to be taken for this research project and patients will only be followed standardized, with special attention for blood pressure measurements, during the first year of life.
Data will be collected prospectively using a case report form. Data will be collected by the peadiatric endocrinologists in the Radboud University Nijmegen Medical Centre after clinical visits of the CAH patients. Data concerning blood pressure levels will be recorded by experienced nurses, working at the paediatric endocrinology department.

24-hour urine collection

24-hour urine will be collected in controls while they are hospitalized. In general this will be from day 0 until day 5. 24-hour urine will be collected in CAH patients during their hospitalization after they presented to the hospital. Prior to every visit to our outpatient clinic parents will be asked to collect 24-hour urine nappies.
Collections can only be carried out with nappies that contain fluid-absorbing granules such as Pampers, Huggies or similar. The same type of nappy should be applied throughout the collection day and parents or nurses should avoid putting creams on the baby*s bottom. A clean nappy of the same size and brand have to be provided. This information will be used to determine the dry weight of the specific nappy. In principle, we can*t make use of nappies that are contaminated with faeces but only can process nappies that contain urine only. Nurses and parents should place water-resting liners on the inner lining of the nappies. If upon changing the nappy only contains urine, both nappy and liner can be put in a collection bag. If the nappy contains faeces than the liner with the faeces should be discarded while the nappy is put in the collection bag. Odd stains and spills of faeces do not represent a problem but a completely soiled nappy can*t be used. The collection bag with the collected nappies will be kept in the -20 C freezer in the Radboud University Nijmegen Medical Centre in a plastic bag that has been labeled with the name and date of collection. The nappy bag will be sent to Birmingham on dry ice and include the dry, clean nappy.
The urine will be extracted from the nappies and prepared for gas chromatography-mass spectrometry (GC-MS) analysis to characterize the urine steroid metabolome in the first weeks of life. The analysis of 24-hour urine steroid metabolite profiles using gas chromatography/mass spectrometry is well established as a diagnostic tool. The GC/MS set-up at the Centre for Endocrinology, Metabolism and Diabetes at the University of Birmingham, UK, allows for the simultaneous identification and quantification of 35 steroid metabolites, and can be used as an integrated read-out of steroid metabolites that specifically accumulate in CAH. Since samples are always run in scanning mode, the traces can be further analyzed for other compounds. GC/MS has proven its role as a pre-eminent discovery tool in clinical steroid investigations even in the era of fast tandem mass spectrometry as it provides the opportunity

to visualize the entire steroid metabolome in one run. In the past, this approach has defined conditions such as AME syndrome, glucocorticoid remediable aldosteronism (GRA), P450 oxidoreductase deficiency (ORD) and apparent cortisone reductase deficiency (ACRD). The profiles obtained from CAH patients will be compared with urine steroid profiles from patients with other forms of inborn primary adrenal insufficiency, which commonly present with early onset mineralocorticoid deficiency during the first days of life.

Study burden and risks

None

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

All newborn patients with a classical form of CAH are eligable for inclusion in this study.

Exclusion criteria

None

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2010
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	20-08-2010
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	NL32566.091.10