Unravelling the mechanism of azoospermia in nephropathic cystinosis

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To clarify the mechanism of azoospermia in male cystinosis patientsTo determine the cause of azoospermia in male cystinosis patients as obstructive or non-obstructive by non-invasive means (clinical examination, reproductive hormonal profile,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON46648

Source
ToetsingOnline

Brief title
Azoospermia in nephropathic cystinosis

Condition

- Metabolic and nutritional disorders congenital
- Nephropathies

Synonym
Nephropathic cystinosis

Research involving
Human

Sponsors and support

Primary sponsor: University Hospitals Leuven, Belgium
Source(s) of monetary or material Support: Grant

Intervention

Keyword: Azoospermia, Nephropathic cystinosis

Outcome measures

Primary outcome

Defining the origin of azoospermia in adult post-pubertal male infantile

nephropathic cystinosis patients in terms of obstructive or non-obstructive

azoospermia.

Secondary outcome

Not applicable

Study description

Background summary

General background
Cystinosis is an autosomal recessive lysosomal storage disorder characterized by widespread lysosomal cystine accumulation and crystal formation in all body tissues. Various endocrine organs are affected.
In a first organized report on reproductive function in male cystinosis patients, primary hypogonadism has been documented in a substantial subset of patients (approximately 70%) (Chik et al., 1993).
Recently, in a small male cystinosis patient cohort study performed by our group, azoospermia was remarkably observed in all of these patients, despite a normal pituitary-testicular axis, early cysteamine treatment and a normal renal function (eGFR) (Besouw et al., 2010). However, testicular biopsy in one of these patients showed a normal spermatogenesis (Johnson score 8 - 9) (Besouw et al., 2010). As primary hypogonadism has shown to be present in a substantial proportion of the adult patients, we can assume that fertility could gradually decrease from the post-pubertal stage onwards, with increasing age.

1. Fertility effects of cysteamine.
Based on in vivo and in vitro data of animal studies as well as studies performed on human subjects, it may be hypothesized that cysteamine treatment could contribute to sub/infertility through (1) endocrine effects, (2) direct spermicide effects, and (3) effects on posttranslational modifications during epididymal sperm maturation.

1.1 Endocrine effects

Animal studies have shown a suppressive effect of cysteamine on gastric somatostatin production (Szabo et al., 1981). Fukuhara et al documented an inverse correlation between gastric density of somatostatin producing cells and plasma somatostatin levels on one hand, and plasma ghrelin levels on the other hand, after cysteamine administration (Fukuhara et al., 2005). These data suggest an indirect stimulation of ghrelin secretion by cysteamine through suppression of somatostatin.

In vitro and in vivo data have suggested a local gonadal effect of ghrelin on Leydig cell proliferation, testosterone secretion and regulation of apoptosis in spermatogenesis (Camninos et al., 2014). In vivo data in human male and female subjects have also identified a systemic effect of ghrelin on the hypothalamic pituitary axis. Suppression of LH and FSH production and increased prolactinemia after ghrelin bolus injection has been clearly documented (Camninos et al., 2014; Kluge et al, 2007; Lanfranco et al., 2008; Messini et al., 2009).

1.2 Direct spermicide effects

The direct effect of cysteamine on sperm function has been demonstrated by a potent dose- dependent reversible inhibition of sheep testicular hyaluronidase (IC50 150 µg/ml), and a moderate reversible inhibition of human acrosin by cysteamine (IC50 370 µg/ml) (Anderson et al., 1997). A weak sperm-immobilizing capacity of cysteamine has been documented in a modified Sander-Cramer test with an IC50 of 16 ± 3.5 mg/ml. A significant spermicidal effect of cysteamine has been observed in a modified Sander-Cramer test when motility is evaluated after 10 minutes, with 80% inhibition of rabbit sperm motility at 10µg/ml cysteamine, and complete inhibition at cysteamine concentrations ranging from 50µg/ml to 500µg/ml (Anderson et al., 1997). Whether cysteamine penetrates the blood-testes barrier and which concentrations are reached in human sperm is unknown.

1.3 Effects on posttranslational modifications

Disulfide bond formation constitutes an important part of the posttranslational modifications taking place during the epididymal sperm maturation process (Sutovsky, 2014). Several organelles in the tail of spermatozoa (e.g. the outer dense fibres, outer mitochondrial membrane, fibrous sheath, and connecting piece) contain sulfhydryl rich groups which undergo oxidation during epididymal transit. The disulphide bond formation in these organelles is important in stabilizing the sperm tail structure and acquiring the normal wave pattern of sperm motility. Since cysteamine is a disulphide bond breaking agent, it can be hypothesized that it might exert a negative effect on these necessary posttranslational modifications.

2. Animal models and cell lines in fertility of cystinosis

Unfortunately, in our previous study we have demonstrated that the male Ctns-/- C57BL/6 murine model is not suitable for unravelling the pathogenesis of infertility in cystinosis since it does not exert an infertility phenotype (Besouw et al., 2012). Also, no other cystinosis animal models with an

infertility phenotype are currently available.

Study objective

To clarify the mechanism of azoospermia in male cystinosis patients

To determine the cause of azoospermia in male cystinosis patients as obstructive or non-obstructive by non-invasive means (clinical examination, reproductive hormonal profile, ejaculated semen analysis, analysis of seminal biomarkers, ultrasonographic biomarkers, urine sampling) in comparison to patients with confirmed obstructive azoospermia (group B) and age-matched healthy control subjects (group C).

Study design

This trial is a prospective, interventional, case-control study.

Study burden and risks

The burden and risks for the subjects involved in this study, are both minimal. The burden exists in having a visit with an Andrology specialist, consisting of a history and clinical examination, a venapuncture, a testicular ultrasound, and making a sperm- and urine sample. Depending on the duration of abstinence prior to making this sperm sample, it can be necessary to make a second appointment for making this sperm sample.
Risks are limited to the (minimal) invasive procedure of a venipuncture; although these risks are not different in nature or severity then in case of a classical venipuncture.

Contacts

Public
University Hospitals Leuven, Belgium

Herestraat 49
Leuven 3000
BE
Scientific
University Hospitals Leuven, Belgium

Herestraat 49
Leuven 3000
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Group A: male nephropatic cystinosis patients:
- Post-pubertal, adult (> 18 years of age) males with infantile nephropathic cystinosis
- Under cysteamine treatment
Group B: control subjects with confirmed obstructive azoospermia
- Patients with confirmed obstructive azoospermia
- Ages: 18 - 45 years old
Group C: healthy control subjects:
- Healthy male donors
- Ages: 18 - 45 years old

Exclusion criteria

Group A:
- Previous chemotherapy
- (pre-/)pubertal boys
- age below 18 years
- unability to deliver consent due to mental disability
Group B, C:
- Previous chemotherapy
- (Pre-/)pubertal boys
- Age below 18 years
- Underlying chronic disorder
- Unability to deliver consent due to mental disability

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:	Recruitment stopped
Start date (anticipated):	01-10-2018
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO

Date:	09-07-2018
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	NL65400.091.18