"Detection of primary hyperoxaluria in patients with recurrent kidney stones"

Published: 21-11-2011
Last updated: 28-04-2024

Diagnosis of patients with primary hyperoxaluria in a cohort of patients with recurrent urolithiasis.

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

Summary

ID

NL-OMON35996

Source
ToetsingOnline

Brief title
DETOX (DETection of OXalate)

Condition

- Metabolic and nutritional disorders congenital
- Urolithiases

Synonym
hyperoxaluria; oxalate kidney stones

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: hyperoxaluria, prevention, screening, urolithiasis

Outcome measures

Primary outcome

Measurement of oxalate, glycolate and L-glycerate in a urine sample, and DNA diagnosis of the AGXT gene for primary hyperoxaluria type 1 or the GRHPR gene for primary hyperoxaluria type 2 if applicable.

Secondary outcome

Estimation of kidney function in patients with recurrent kidney stones

Study description

Background summary

Kidney stones or urolithiasis is a frequent occurring problem. Approximately 0.5% of the Dutch population suffers from episodes of urolithiasis (Statistics Netherlands 2010). A subset of patients with recurrent kidney stones may develop end-stage renal disease as a consequence of ongoing calcification of the tubuli. Early recognition of specific causes of urolithiasis may prevent renal damage. This is observed in patients with a form of primary hyperoxaluria (type 1 or type 2) (Danpure and Rumsby 2004). These are autosomal recessive inborn errors of glyoxylate metabolism. Deficiency of either the liver specific enzyme AGT in primary hyperoxaluria type 1 or the cytosolic enzyme GR/ HPR in primary hyperoxaluria type 2 leads to elevated endogenous production of oxalate. The mutated AGXT gene leads to primary hyperoxaluria type 1 and the mutated GRHPR gene leads to primary hyperoxaluria type 2. The primary hyperoxalurias are rare metabolic disorders, with 80 patients diagnosed in The Netherlands so far (van Woerden et al. 2003, and follow-up study, submitted 2011). The primary hyperoxalurias result in the generation of calcium oxalate depositions in the kidneys, with clinical signs and symptoms of urolithiasis or nephrocalcinosis (i.e. diffuse deposition of calcium oxalate precipitations in the renal parenchyma). Kidney function becomes impaired due to ongoing oxalate deposition in the kidney parenchyma. Irreversible end-stage renal disease may ensue. Conservative therapy by means of hyperhydration or crystallization inhibitors, such as citrate prevents renal damage. However, conservative treatment is only successful when started before decline of renal function.

The two most common forms of primary hyperoxaluria are defined by the so-called Gly170Arg or Phe152Ile genotype in primary hyperoxaluria type 1. Patients with these genotypes show decline of oxalate excretion up to normal values upon treatment with pyridoxine, vitamin B6 (25 mg daily). Pyridoxine serves as the co-factor of the AGT enzyme, which is partially deficient in these genetic subgroups. Pyridoxine treatment leads to disappearance of symptoms and preservation of kidney function (Milliner et al. 1994, van Woerden et al. 2004). This beneficial effect of pyridoxine has been confirmed in all other primary hyperoxaluria cohort studies thereafter (Monico et al. 2005, Harambat 2010). Following our epidemiologic survey, published in 2003 (van Woerden et al.. 2003) we observed a large delay between the date of occurrence of symptoms and date of diagnosis of primary hyperoxaluria. Therefore, we suspected underdiagnosis of primary hyperoxaluria in The Netherlands. In the Dutch cohort of patients with primary hyperoxaluria, especially adult patients presented in end-stage renal disease despite the presence of symptomatic urolithiasis for years. Late diagnosis, even after kidney transplantation which was performed because of end-stage renal disease of unknown origin, was also shown in a recent French cohort study on patients with primary hyperoxaluria (Harambat et al.. 2010). As early diagnosis and treatment is extremely important to start treatment timely and preserve renal function, diagnostic screening in patients with recurrent urolithiasis or unexplained decline of renal function should be improved. A screening study for patients with hyperoxaluria in the General Laboratory of Clinical Chemistry in the AMC, Amsterdam, has found a patient with the pyridoxine sensitive form of primary hyperoxaluria type 1 (van Woerden et al.. 2007). A recent follow-up study of the Dutch hyperoxaluria cohort was performed (van der Hoeven et al.. 2011, submitted). It demonstrated end-stage renal disease in the vast majority of patients diagnosed with primary hyperoxaluria at adult age, despite the presence of the pyridoxine sensitive genotype. Diagnosis of primary hyperoxaluria in patients with a history of recurrent urolithiasis, treated in a urology center, which could have been prevented by early conservative treatment, motivates us to initiate the current study. After assembly of the cohort of patients with primary hyperoxaluria in 2003 by investigation of all nephrologists in The Netherlands, the current proposal targets urology specialists as to focus on patients with recurrent episodes of urolithiasis.

To date, no other studies have investigated primary hyperoxaluria as an overlooked cause of recurrent episodes of urolithiasis. In view of the potential prevention of renal insufficiency, finding patients with primary hyperoxaluria by our proposed study entitled *Detection of primary hyperoxaluria in patients with recurrent kidney stones* (short title *the DETOX study*) would strongly improve conservative management of patients with urolithiasis. This would lead to a new diagnostic approach, including metabolic urine screening for patients with recurrent urolithiasis.

Study objective

Diagnosis of patients with primary hyperoxaluria in a cohort of patients with recurrent urolithiasis.

Study design

Patients will be recruited at the department of urology of the OLVG, Amsterdam. All patients who underwent a procedure for kidney stone removal by means of endoscopy or ESWL (extra corporeal shock wave lithotripsy) in 2010 will be included. The time frame is used to estimate number patients that need to be screened annually at the department of urology for diagnosis of primary hyperoxaluria. Exclusion criteria are: secondary hyperoxaluria due to short bowel disorders, or inflammatory bowel disorders. All other patients will be approached for diagnostic research for primary hyperoxaluria by means of urine screening.

Patients will be approached in a two-step approach in accordance with the procedure that was followed in our screening study in 2007, which was at that time approved by the Institutional Review Board of the AMC, Amsterdam. Candidate participants will be sent a request to participate in a study that investigates urolithiasis. After obtaining a positive answer from them, a letter with all study information will be sent to candidate participants to obtain informed consent. After obtaining informed consent of the participants, they will be asked to deliver a collection of urine in a dry container at the laboratory for analysis of oxalate, glycolate and L-glycerate for diagnosis of primary hyperoxaluria. An 8 ml EDTA blood sample will be obtained for DNA diagnosis to determine genotype of primary hyperoxaluria once urine test confirms a diagnosis of primary hyperoxaluria.

Study burden and risks

Minimal risks of phlebotomy for 8 ml blood collection. This is only performed if primary hyperoxaluria is strongly suspected by urine investigation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with recurrent episodes of kidney stones

Exclusion criteria

Secundary hyperoxaluria caused by short bowel syndrome or inflammatory bowel disorders.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2011
Enrollment:	250
Type:	Anticipated

Ethics review

Approved WMO Date:	21-11-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL36032.100.11