Determination whether the lack of functional AQP2 in kidneys of patients suffering from nephrogenic diabetes insipidus induces cyst formation

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Does the lack of the Aquaporin-2 water channel cause cyst formation in patients suffering from nephrogenic diabetes insipidus?

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON41471

Source
ToetsingOnline

Brief title
Determination of renal cyst formation in patients that lack functional AQP2

Condition

- Renal and urinary tract disorders congenital
- Genitourinary tract disorders NEC

Synonym
Nephrogenic diabetes insipidus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Afdeling Fysiologie;Radboud universitair medisch centrum te Nijmegen

Intervention

Keyword: AQP2, Cyst, Kidney, NDI

Outcome measures

Primary outcome

The main study parameter is the presence or absence of microcysts in kidneys.

Secondary outcome

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Study description

Background summary

The Aquaporin-2 (AQP2) water channel is expressed in the renal collecting duct and is essential in the vasopressin-regulated reabsorption of water from pro-urine and concentration of urine. The essential role of AQP2 in this process is illustrated by the fact that mutations in the AQP2 gene, leading to non-functional water channels, is the cause of autosomal congenital nephrogenic diabetes insipidus (cNDI)(1-5). In cNDI, the kidney is unable to concentrate urine, despite increased vasopressin levels, resulting in voiding of large volumes of low-osmotic urine (polyuria) and, as a consequence, polydipsia (excessive thirst). In a recent publication in the renommated Journal of the Americal Society of Nephrology (impact 9.0), evidence has been gathered leading the authors to postulate that AQP2 is, besides preventing NDI, also essential to prevent development of renal microcysts(6). The argumentation and evidence the authors supply for this are that:
1) Inactivation of AQP2, AQP3 or AQP4 in transgenic knockout mice leads in all cases to NDI, but that only mice with AQP2 mutations develop renal cysts.
2) Cells (LLCPK and MDCK), which are stably transfected with AQP2 show, during cell proliferation, binding to integrin, a protein located in the basal matrix and essential for cellular polarization. These authors suggest that this binding is important for collecting duct cells to migrate in a particular direction, which would be of relevance for tubule formation.

We have strong arguments that AQP2 is not involved in cell migration over the basal matrix and that the lack of functional AQP2 does not lead to cyst

formation. Our arguments/indications are the following:
Ad 1) mice with congenital inactivating mutations in the AQP2 gene die within 1-2 days postnatally, because of severe dehydration, whereas mice with congenital AQP1, AQP3 or AQP4 mutations survive well, but have NDI (7-11). The lack of AQP2 thus gives a larger polyuria than the lack of AQP1, AQP3 or AQP4. With humans, this difference in aquaresis is similar, but less severe: humans with AQP2 mutations survive, but suffer from cNDI, whereas humans with AQP1 or AQP3 mutations have no problem with their diuresis (12, 13).
Ad 2) When cells are polarized, they do not divide (proliferate) and proliferating cells are thus not polarized. The cells used by Chen et al do express AQP2 at all stages of cell proliferation, because they have been stably transfected. From our analysis with mpkCCD mouse kidiney collecting duct cells, which express endogenous AQP2 upon stimulation with vasopressin, it is clear that AQP2 is only expressed in collecting duct cells when they are polarised, but not when they are non-polarised, i.e. proliferative (see figure 1). Based on our data, using a proper physiological cell model in contrast to Chen et al, AQP2 is thus not available to bind integrin during proliferation and thus cannot be involved in guided growth along the cellular matrix and tubule formation.
Ad 3) In the >15 years that I have performed research on cNDI, I have never encountered a clinician stating that he/she has observed cysts in the kidney of a cNDI patient.
Our argumentation and data indicate that reduced polarization (and thus increased proliferation) of collecting duct principal cells leads to reduced expression of AQP2 and diuresis, but not that AQP2 itself is needed to prevent cyst formation. The absence of microcysts in kidneys of cNDI patients with AQP2 gene mutations provides the answer.

Further fundament and clinical relevance:
Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease leading to chronic kidney failure and, eventually, lifelong dialysis or, kidney transplantation. Similarly, nephronophthisis (NPHP) is the most common cause of chronic kidney failure in children ADPKD is caused by inactivating mutations in the polycystin-1(PC1) gene. Together with NPHP proteins, they are involved in cilia formation. The first signs of development of these diseases is increased diuresis, despite increased AVP levels. As ADPKD and several NPHP forms mainly start to develop in the collecting duct, the observed diuresis indicates to reduced AQP2 levels. Recently, it has been shown that mutations in PC-1 lead to increased cell proliferation (14). Based on the data from Chen above, the diminished AQP2 expression could contribute to the cyst formation found in ADPKD (and NPHP). If our proposed analysis of the kidney of NDI-AQP2 patients shows that the lack of AQP2 does NOT lead to cyst formation, a contribution of AQP2 to cyst development in ADPKD and NPHP can be excluded. Considering the severity of ADPKD and NPHP, this knowledge will not only be of fundamental knowledge, but will also be of use in the development of appropriate therapies for ADPKD and NPHP.

Why MRI instead of ultrasound?:
In sections of the kidneys of mice transgenic for AQP2 mutations, microcysts were detected. Analysis of the kidneys of NDI patients need to be done non-invasive. To be able to strongly establish whether kidneys of NDI patients due to AQP2 mutations have microcysts, MRI is needed instead of ultrasound, as this non-invasive technique has a resolution high enough to detect microcysts.

Selected population:
The only strong evidence whether AQP2 is involved in cyst formation is to analyse whether humans lacking functional AQP2 have renal,cysts. Humans lacking functional AQP2 are congenital NDI patients. Though this is a rare congenital disease, the paediatrics dept of the Radboud Univ. Medical Center has been a referral center for NDI patients for decades and has contacts with several such patients.

Study objective

Does the lack of the Aquaporin-2 water channel cause cyst formation in patients suffering from nephrogenic diabetes insipidus?

Study design

This observational study will be carried out in the Radboud university medical center. Since this study is only used to determine whether there is a presence of microcysts and since autosomal congenital nephrogenic diabetes insipidus with mutations in the AQP2 gene is quite unique, 2 to 5 patient will be asked to participate. Eligible patients will be fully informed about the reasons behind this observational study and so the need of a MRI. After having obtained their written informed consent about participating in the study and the availability of their kidney images for scientific publications, an MRI appointment will be scheduled with at the radiology department.

At the radiology department, the MRI technicians will position the patient in the MRI, supine with feet first and a body phase array coil to improve image resolution. The MRI of the kidneys will be made without contrast agent. If wished by the patient or relatives, the patient can practice the MRI with pedagogical assistance upfront.
Since the kidneys have respiratory motion, the images will be made with fast imaging techniques. If possible for the patient the scan will be performed during one expiration because the kidney position is more constant in expiration than in inspiration. If the sequence is too long to perform in one breath-hold respiratory gating can be used. With this technique a navigator pulse is used which monitors diaphragm motion to trigger when images can be made. A phased array body coil is used to improve the signal-to-noise ratio since high contrast is important in visualizing microcysts, a high signal-to-noise ratio is essential. The patients arms should be raised above

the head to prevent aliasing in coronal imaging. Images will be made with a 1,5 or 3 Tesla system.
The following sequences will be made:
- Coronal T2-weighted sequence, serving as a localizer, but also supplying valuable T2-weighted information. The limitation of this sequence is a relatively low signal-to noise ratio.
- Axial T2-weighted turbo spin echo sequence with fat suppression to provide more detailed T2-weighted information. The T2-weighted sequence is especially helpful in characterizing cysts.
- Axial T1-weighted gradient echo sequence preferably as a dual-echo sequence. Many solid renal lesions, like cysts, are hypointense compared to the renal parenchyma on T1-weighted images, but lesions with high protein content may show hyperintense signal.

The MRI will take about 30 minutes after it is made, the radiologist will interpret the obtained images and make a report. This report will be send to the researchers involved and general practitioner of the patient as well.

Study burden and risks

Adverse events that can be expected are primarily related to the process acquiring the MRI.
These events are for instance; claustrophobia, dizziness, and a local very minimal rise in temperature of the upper surface of the body (skin).

This study is fundamental in nature and will not have clear benefits for the participant.
When the MRI is made, more could be known about the condition of the patient*s kidneys. There is as well a small change of unexpected findings.
A MRI is a standard imaging technique which has a relatively low discomfort for the patient.
During the MRI patients can get scared because of the loud noise of the machine or the narrow space in which they are lying this could give problems when a MRI needs to be made in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Men and woman not known to be pregnant
Congenital nephrogenic diabetes insipidus with a proven mutation of the AQP2 gene
Age > 12 years

Exclusion criteria

- Metal implants
- Pacemaker
- Intracranial aneurysmal vascular clips
- Small metal particles/splinters
- Cochlear implants
- Old heart valve implants (the ones placed after 2001 are often MR-compatible)
- Implants
- Claustrophobia
- All sorts of devices like bladder stimulators, neurostimulators and insulin pumps
- Dental prosthesis/dental braces
- Telemetric heart rate monitor
- Metal tissue expanders
- Known pregnancy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-12-2016
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	19-04-2016
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	NL46757.091.15