Vasopressin and copeptin
Heida, Judith

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Chapter 2

Autosomal dominant polycystic kidney disease
This chapter will familiarize the reader with Autosomal Dominant Polycystic Kidney Disease (ADPKD) to provide a background for the chapters that form the third part of this thesis. In particular the role of vasopressin in the pathophysiology of ADPKD will be discussed.

Clinical presentation and course of the disease

ADPKD is a genetic disease that is characterized by continuous development and growth of cysts in both kidneys. ADPKD is the most common hereditary kidney disorder worldwide. The prevalence of ADPKD is estimated at 4 per 10,000 persons. Over the course of a lifetime kidney size increases exponentially. To illustrate, young ADPKD patients aged between 15 and 24 years have a total kidney volume of approximately 700 mL and this volume continues to increase to a mean of 1250 mL in patients aged 35 to 45 years. In comparison, healthy persons have a total kidney volume of approximately 270 to 355 mL.

ADPKD is characterized by early onset of hypertension and increased urinary output due to an impaired urine concentrating capacity. Theretofore, a decrease in glomerular filtration rate follows. The glomerular filtration rate is estimated to decrease around 3 mL/min/1.73m² per year in adult ADPKD patients, leading to end-stage kidney disease at an average age of 58 years. These numbers are population means and do not reflect the variability in the course of disease amongst patients. Approximately 70% of all ADPKD patients will reach end-stage kidney disease for which renal replacement therapy is required.

As cysts grow in number and size, other symptoms develop. Cysts can become infected and bleeding or rupture of cysts can occur. These events can be accompanied with sudden onset of pain. Another frequent cause of disease-related transient pain is nephrolithiasis. ADPKD predisposes to the formation of kidney stones. This is thought to be the result of urinary stasis caused by the abnormal renal architecture in combination with disease associated metabolic disorders. In addition to these transient pain events, the enlarged cystic kidneys can cause chronic pain as well. Oppression of surrounding tissue, and especially the kidney capsule, is postulated to cause this lasting pain sensation.

ADPKD is primarily a kidney disease, however, extra-renal complications should not be overlooked. Cysts can develop in other organ tissues such as liver, pancreas, seminar vesicles and ovaries. Increased liver volume due to cystic expansion is an important contributor to ADPKD related gastrointestinal complaints. These complaints are present in approximately 60% of the patients with later stage disease and include a bloating sensation, obstipation and a decrease in appetite and consequent weight loss. Even though hepatic tissue can be affected by excessive cysts growth, liver failure is much less common than kidney failure. Other complications of ADPKD are vascular abnormalities, including intracranial aneurysms. ADPKD patients consequently have an increased risk of subarachnoid bleeding and subsequent neurological comorbidity.

Diagnosing ADPKD

Although it is a hereditary disease, the diagnosis of ADPKD is based on the result of a clinical evaluation and not genetic testing. The genomic complexity of the mutated genes has made implementation of genetic testing in clinical practice rather difficult. Instead, standardized clinical criteria are used that take into account the number of kidney cysts at a certain age, whether or not the causative genetic mutation of affected family members is known and imaging method used (ultrasound versus CT or MR imaging). Test characteristics of this clinical algorithm are excellent, with a specificity of 100% and a sensitivity between 70 and 100%, depending on patient characteristics.

Genetic background and cellular pathophysiology

ADPKD is typically caused by a mutation in either one of two genes: *PKD1* or *PKD2* located on chromosome 16 (16p1.3) and chromosome 4 (4q21), respectively. In approximately 80% of ADPKD patients a mutation in the *PKD1* gene is found and in 15% of the patients the *PKD2* gene. Mutations in other genes causing a cystic phenotype that are inherited in an autosomal dominant fashion, as for example in the *GANAB* gene, are less frequent.

In some families, the underlying genetic mutation has not yet been identified. The *PKD1* and *PKD2* genes code for the proteins polycystin 1 and polycystin 2, respectively. Together polycystin 1 and 2 form a cell membrane complex on the apical side of the renal tubular cells. It forms part of a hair-like organelle called the primary cilium. Polycystin 1 is a mechanosensor. Increase of the flow velocity of fluid in the tubular lumen is sensed by polycystin 1, which then induces calcium influx into the tubular cells through polycystin 2. This increase in intracellular calcium reduces the activity of the enzyme adenylate cyclase, a process that has shown to be vital for preserving the integrity of the cell. Adenylate cyclase converts inactive adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP is a signaling nucleotide that activates various regulatory pathways essential for cellular functioning and growth. There are a number of endocrine and paracrine factors that stimulate activity of adenylate cyclase through binding to a cell membrane receptor. The polycystin complex provides an essential counterbalance effect to these signals. Without properly working polycystin proteins, as is the case in ADPKD, the break on the activity of adenylate cyclase is absent. The result is a disproportional increase of cAMP levels, which causes several proliferative pathways such as the Ras/Raf/MEK/ERK and mTOR pathways to promote cystic expansion of the tubular cells. In addition, the rise in cAMP also induces chloride and fluid secretion into the cysts via activation of cystic fibrosis transmembrane conductance regulator (CFTR) channels.

It is important to note that not all tubular cells of ADPKD patients develop cystic properties. At cellular level a second somatic mutation in the other non-affected allele of *PKD1* or *PKD2* is required to develop a cystic phenotype. After this second hit, the number of functional polycystin complexes falls below a critical level. Lastly, in addition
to mutations of PKD1 and PKD2 more causative genetic alterations are recognized, for example of the GANAB gene. The protein transcript of GANAB, glucosidase II, is important for the functionality of the polycystin proteins. Glucosidase II is an enzyme that is involved in the maturation and localization of polycystin 1,20

**Vasopressin, although essential to the kidney, is detrimental in ADPKD**

As mentioned in the first paragraph, one of the early consequences of cystic expansion of the kidneys of ADPKD patients is a decreased capacity to form concentrated urine.3,9,13

To explain the decline of concentration capacity in ADPKD patients, it is important to emphasize that in addition to translocation of aquaporin channels to the cell membrane after binding of vasopressin to the V2 receptor, the process of forming concentrated urine depends largely on the anatomic organization of tubuli and capillaries within the nephron. In ADPKD, multiple cysts disrupt the anatomic architecture of the nephron and thus the build-up of the osmotic gradient, thereby causing concentrating capacity to decline. When kidneys fail to bring water back into the circulation to a sufficient degree to restore plasma osmolality, vasopressin binding to the V2 receptors is intensified to compensate. V2 receptors are membrane receptor that operate through induction of adenylyl cyclase activity and thus stimulate an increase of intracellular cAMP. Therefore, receptor activation by vasopressin directly contributes to disease progression of ADPKD. Development and growth of more cysts cause the concentrating capacity to decline further, thus increasing the stimulus for more vasopressin to be released from the pituitary. This vicious circle is presented in Figure 1.

![Figure 1. Schematic presentation of pathophysiological changes in ADPKD patients that result in elevated plasma vasopressin concentration and the consequences for disease progression. Adapted from Meijer et al.](image)

**Vasopressin pathway as treatment target**

The advances in understanding the pathophysiology of ADPKD, and especially the role of vasopressin, have led to the discovery of a drug that can slow disease progression. This drug, the vasopressin V2 receptor antagonist tolvaptan, prevents binding of vasopressin to renal tubular cells by competitive antagonism. Two international multicenter randomized controlled trials have demonstrated that tolvaptan is able to decrease the rate of kidney function decline with 26 to 35% in ADPKD patients with early-stage as well as later-stage disease.41,42 On average, four years of treatment with tolvaptan will postpone the onset of end-stage kidney disease by one year.

Treatment with tolvaptan has an obvious downside. Preventing vasopressin binding to the V2 receptor on the collecting duct cells induces a nephrogenic diabetes insipidus, with as consequence an average urine volume of 6 to 8 liters per day. This is a considerable burden for patients. Polyuria causes a permanent thirst sensation and disturbed night rest, thereby negatively affecting quality of life and reducing treatment adherence. In addition to polyuria, prescription of tolvaptan might have off-target effects attributable to a rise in plasma vasopressin concentration. Since tolvaptan limits the antidiuretic effect of vasopressin drastically, there is no negative feedback on the secretion of vasopressin by the pituitary, and therefore its plasma levels rise significantly. In this state, vasopressin can bind to other types of vasopressin receptors, the V1 and V3 receptors, for tolvaptan is a selective V2 receptor antagonist. These additional effects of vasopressin have been discussed in chapter 1.
Prediction of disease progression

It is well-recognized that disease severity and rate of progression are highly variable between patients with ADPKD. Questions from patients regarding their perspectives are often difficult to answer. Accurate predictors are not only sought for personal reasons, such as family planning, the introduction of tolvaptan has created an additional incentive. Given that use of this drug significantly impacts quality of life, only those patients with a high likelihood of rapid disease progression should be selected for treatment. Therefore, studies on the prediction of future disease progression have gained even more priority in the last few years.

In the field of nephrology in general, the most prominent clinical biomarker to evaluate severity of kidney disease is the estimated glomerular filtration rate (eGFR). In ADPKD however, the predictive value of eGFR for future renal function decline is questioned. In contrast to the kidneys’ decreased capacity to concentrate urine or to control blood pressure correctly, the glomerular filtration rate of ADPKD patients remains unaffected during the early stages of the disease. It is only in later stages of the disease, when quantity and size of the cysts cause the number of functioning nephrons to decline, that glomerular filtration rate decreases. To be able to assess kidney damage in early stage disease, other biochemical markers of kidney damage have been assessed. Urinary markers such as albumin as measure for glomerular damage, β2-microglobulin for proximal tubular damage and monocyte chemotactic protein-1 as indicator of inflammatory reaction have shown promise as predictive measures. Interpretation of their values for the individual patient needs to be defined clearly before practical application is possible.

Secondly, given that ADPKD is a disease with genetic variability, the predictive value of mutation type has also been a topic of interest in search for disease progression markers. In general, if the disease is caused by a mutation in PKD1 it will progress faster than PKD2. Patients with a truncating mutation have a worse prognosis than patients with a non-truncating mutation. This suggests that environmental factors are important as well. To combine genetic information with adjustment for environmental effects the PRO-PKD score was conceived. Likelihood of rapid disease progression is estimated by granting points according to mutation type and for onset of hypertension before the age of 35 years and first urological event (macroscopic hematuria, flank pain or cyst infection) before the age of 35 years. Inherent to this manner of scoring is that patients younger than 35 years cannot be assessed properly. Moreover, at present genetic analysis is not routinely performed clinical practice, as it is not mandatory for diagnosis and in general too expensive. Predictive biomarkers that are widely available in clinical practice might therefore be more useful.

Finally, kidney size and especially rate of growth of kidney size are also used to predict future disease progression. An increase in kidney size of five percent or more per year indicates a rapidly progressive disease. However, repeated imaging is often not available. Therefore, a clinically meaningful scoring system was devised, the Mayo hTKV classification. This classification system allocates a patient to either one of six risk groups (A to E or atypical) based on their height adjusted total kidney volume indexed for age.

Although weighting the information provided by these various predictive biomarkers can give an indication of the future for the individual ADPKD patient, their combined predictive value is far from perfect. Therefore, the search for additional predictive markers continues.

Future perspectives for ADPKD patients

One perspective for change in clinical practice in the near future is the increased availability of genetic testing. These tests are becoming less time consuming and therefore more affordable. Although in most cases the diagnosis of ADPKD is fairly straightforward due to the impressive phenotype, sometimes it is challenging when it comes to patients who are the first suspected case in their family, either due to a de novo mutation or limited medical information on deceased family members. Given that approximately 15% of patients have a de novo mutation, access to genetic testing might prove a valuable addition to the current practice.

Finally, various drugs are currently being tested as novel therapy, such as metformin (ClinicalTrials.gov identifiers NCT02656017 and NCT0290391t), pravastatin (NCT04284657 and NCT03273413) and venglustat (NCT03523728). Whether these might prove to be as effective, or rather still, even more efficacious than tolvaptan, is yet to be seen.
References


Part 1

Measurement of copeptin as marker for vasopressin