Patients with autosomal dominant polycystic kidney disease under chronic hemodialysis display thirst disturbance

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Background and Objectives

- **ADPKD** :
  - ✓ Most common inherited nephropathy caused by the mutation of *PKD1* or *PKD2* genes
  - ✓ Characterized by the development of large and numerous fluid-filled cyst in the renal parenchyma leading to chronic kidney disease.
- Cyst growth is activated by high level of intracellular **cAMP** in renal tubular cells :
  - ✓ cAMP level is high in ADPKD patients due to the functional loss of polycystin due to *PKD* genes mutation
  - ✓ cAMP level is highly influenced by the AVP pathway and its peripheral interaction with V2R
- **AVP pathway**:
  - ✓ AVP is centrally secreted by neurons in the supraoptic and paraventricular nuclei of the hypothalamus and is liberated in the posterior pituitary, in conditions of dehydration and volume depletion
  - ✓ V2R antagonist (tolvaptan) is thought to slow down ADPKD development
  - ✓ TEMPO 3:4 and 4:4 clinical trials demonstrated that tolvaptan attenuate CKD progression in ADPKD patients
- Both central and peripheral **defects in AVP homeostasis** have been reported in ADPKD with:
  - ✓ Blunted increase in plasma levels of AVP in response to elevated plasma osmolarity (central defect)
  - ✓ Higher plasma levels of AVP concentration in comparison to urine osmolarity
- **Thirst**:
  - ✓ Is an important part of the regulation of body fluid balance
  - ✓ Is triggered by slight changes in blood osmolality which induce AVP-mediated water conservation and consumption
  - ✓ Polycystins have been located in regions of the central nervous system implicated in thirst

Therefore, one may question the feeling of thirst in ADPKD patients. In this study, we used a surrogate marker of thirst (i.e. the interdialytic weight gain) in patients under chronic hemodialysis (HD), to assess thirst in ADPKD versus age-, gender- and weight-matched controls.

Methods

- Retrospective identification of 14 ADPKD patients and 14 well-matched control patients undergoing chronic hemodialysis (i.e. for more than 3 month) between January 2010 and December 2015 at the University of Liège Hospital
- ADPKD diagnosis relied on the conventional definition based on imaging criteria
- Systematic review of all medical files to isolate clinical and biological parameters

Limitations

- **Retrospective** and **monocentric** design of the study
- Low **number** of patients (but more than 5000 hemodialysis sessions)
- No assessment of the **observance** to diet recommendations and fluid restrictions

Results

Caracteristics of the ADPKD and control patients

	Sex	Age (years)	Dry weight (kg)	HD vintage (months)	Median residual diuresis (ml)	Interdialytic weight gain (kg)	Pre-dialytic natremia (mM)
ADPKD	8 women	58 ± 13	67.6 ± 12.6	26.4 ± 21.5	100 ± 550	1.49 ± 0.94	140±3.5
Control	8 women	63 ± 15	67.5 ± 12.5	26.5 ± 16.5	300 ± 850	1.57 ± 1.08	137±3.2
						p, 0.003	p, $1.06\ 10^{-26}$

- Chronic hemodialysis was routinely performed thrice weekly using isonatremic dialysate
- Diabetes mellitus diagnosed in 3 ADPKD patients and 7 control patients. Mean glycated hemoglobin levels below 7.5% in all cases
- Hemoglobin levels in the recommended targets in all patients
- Angiotensin-converting-enzyme inhibitors or sartans was similar in both groups (5 in ADPKD and 4 in controls)
- No chronic diarrhea or extra-renal fluid losses documented among the 28-patient cohort
- In control patients, etiology of ESRD :
  - ✓ Hypertensive glomerulosclerosis (n=5)
  - ✓ diabetic nephropathy (n=4)
  - ✓ chronic pyelonephritis and anomalies of the urinary tract (n=4)
  - ✓ IgA nephropathy (n=1)
- Two nephrectomies and one failed kidney transplantation in the control patients, none in the ADPKD patients

Discussion

- Interdialytic weight gain is used as a parameter of salt and fluid intake in patients under chronic HD
- Elevated plasma levels of Na+ and osmolality are regarded as ones of the main triggers of thirst
- Interdialytic weight gain is lower in ADPKD patient in comparison to well-paired controls, despite higher natremia :
  - ✓ This observation probably reflect lower fluid intake in ADPKD patients because no significant variance was observed between groups regarding residual diuresis and extra-renal losses
  - ✓ The observed discordance between low fluid intake and hypernatremia supports a central defect in AVP secretion in ADPKD patients under chronic HD
  - ✓ This observation may be linked to the interaction of polycystins with osmoreceptors as polycystins are expressed :
    - ❖ in the suprachiasmatic and paraventricular nuclei which are responsible for AVP synthesis and release
    - ❖ in the subfornical organ (SFO) which does not have a blood-brain barrier and is responsive to osmolarity, intravascular volume and various hormones
  - ✓ Osmoreceptors processes information about fluid balance and participates in various homeostatic responses, including the generation of thirst and release of AVP

Further interventional investigations are required to decipher the pathophysiology of thirst and fluid homeostasis in ADPKD patients

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Renal development & cystic diseases

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