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Editorial Comment

EDITORIAL COMMENT

A need for a systematic genetic evaluation of hereditary polyuric patients

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In this issue of *CKJ*, Wong *et al.* [1] present a 44-year-old patient with life-long polyuria and polydipsia, a presumed diagnosis of autosomal dominant nephrogenic diabetes insipidus (NDI), progressive dilation of the urinary tract and obstructive nephropathy leading to renal failure. High volume polyuria was observed immediately following a successful renal transplant, and urinary osmolality increased with desamino-D-arginine vasopressin (dDAVP), therefore, the previous diagnosis of autosomal dominant diabetes nephrogenic insipidus was false.

The purpose of this editorial is to invite physicians to use modern molecular tools, including genetic analysis, to reassess old diagnoses. This is certainly useful for this transplanted patient bearing, with other affected members of his family, a mutation in his *AVP* gene responsible for autosomal dominant central diabetes insipidus rather than having NDI as previously thought. This hereditary form of central diabetes insipidus is easily treated with dDAVP; this will decrease urine output to less than 2 L per day in an adult and prevent large dilation of the urinary tract and obstructive nephropathy with renal failure, a complication observed with long-term increases in urinary output including psychogenic polydipsia [2], and nephrogenic [3, 4] and central diabetes insipidus [5].

This is an exceptional case, but my team (D.G.B.) had a similar experience with two unrelated cases. In the first case, I was consulted by a hematologist (L.R.) concerning a male patient with a presumed diagnosis of X-linked NDI, end-stage renal failure and bleeding diathesis, which improved with large doses of dDAVP. The patient demonstrated a large increase in factor VIII and von Willebrand factor following dDAVP and had a polyuric son. Since there is no male-to-male transmission in X-linked diseases and since, in X-linked NDI, there is no function of vasopressin V2 receptors not only on principal collecting duct cells but also on endothelial cells [6], the diagnosis could not be X-linked NDI [7]. Here, my team identified a new *AVP* mutation, G88V, in father and son, probably responsible for the disease since the other disease-causing mutations, G88S and G88R, had been identified previously [8]. The transplanted patient and his affected son have since been treated successfully with dDAVP. In the second case, a nephrologist (J.L.-G.) also observed a patient with chronic kidney disease secondary to obstructive nephropathy thought to be secondary, also here, to X-linked NDI, and immediately developing a dDAVP-sensitive polyuria after a kidney transplant. Sequencing of his *AVP* gene revealed a splicing variant segregating with the polyuric phenotype in this large family reclassified as autosomal dominant central diabetes insipidus. Misdiagnoses have also led to chronic renal failure due to obstructive nephropathy. With dDAVP administration, regression of dilation has been observed in central diabetes insipidus [5] and frequent urination and double voiding urinary dilation also decreases in NDI [9, 10].

My team is sequencing, at no charge, four small genes responsible for hereditary polyuric disorders: *AVP* for central autosomal dominant and recessive diabetes insipidus, *AVPR2* for X-linked NDI, *AQP2* for autosomal dominant and recessive NDI, and *KCNJ1* for Bartter syndrome type II. These sequencing results could also be obtained easily from genetic consultants across North America, Europe, and large countries in the East including Japan [11] and China. A detailed phenotype is of critical importance: you must capture the age of the first polyuro-polydipsic signs and symptoms: hereditary NDI patients bearing *AVPR2*, *AQP2* or *KCNJ1* mutations are polyuric at birth and at risk of severe dehydration episodes, they are rarely missed. *KCNJ1* mutations also present with polyhydramnios during the pregnancy leading to their birth [12], therefore a polyuric child + polyhydramnios

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from a possibly inbred family is a tell talesign of Bartter type II [10]. The identification of a 'mild' *AVPR2* mutation like V88M is also of importance since the polyuric phenotype associated with this mutation decreases during dehydration or during the administration of dDAVP [13]. In addition, patients bearing the AVPR2 mutations p.A37P, p.D85N, p.R104C and p.Y128S or the AQP2 mutations p.R254Q and c.763_722del have also been reported to be 'effectively' treated with dDAVP [11].

Central autosomal dominant diabetes insipidus can easily be missed since the first polyuric manifestations occur after the first year of life. Polyuria in toddlers is usually perfectly compensated by thirst and the polyuro-polydipsic manifestations could be perceived as normal or 'running in the family'. In the magnocellular cells manufacturing vasopressin, neurophysin and copeptin coded by *AVP*, the mutant allele will produce a misfolded pre-pro AVP protein with progressive 'amyloid-type' accumulation and death of the vasopressin-producing cells, a classical gain-of-function of an autosomal dominant disease where the normal *AVP* allele cannot be expressed because of the magnocellular death [14].

Evaluation of a polyuric patient could be done easily by obtaining a 24-h urine collection for volume and urine osmolality and excluding glucosuria or other causes of osmotic diuresis [15]. Long dehydration tests should not be done in severely polyuric patients who are at risk of dehydration, and we prefer to do a short dehydration test with a plasma sodium always lower than 145 mEq/L followed by oral administration of water and administration of 1–4 μg microgram sc dDAVP. Also, dehydration tests should be done only if hourly plasma sodium level results are available within 1 h of sampling. Urine volumes and

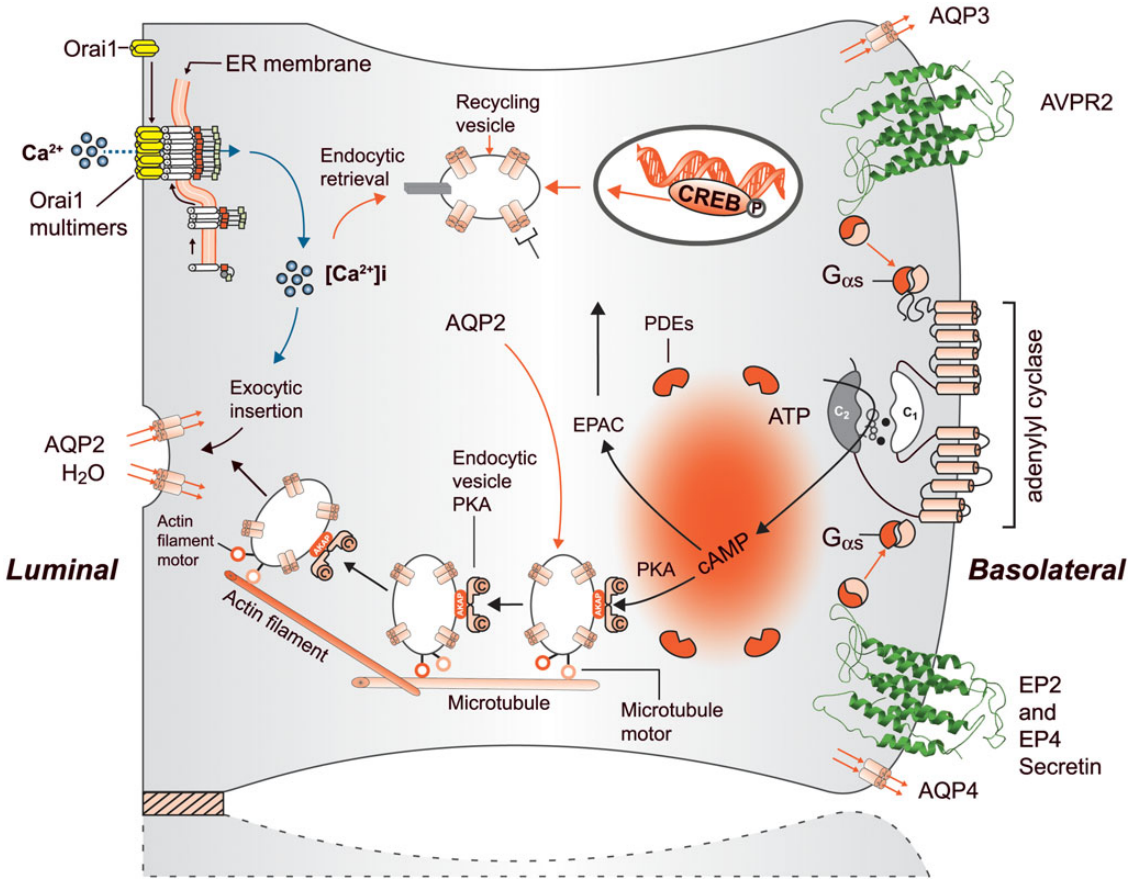

Fig. 1. Schematic representation of the effect of arginine vasopressin (AVP) to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V_2 receptor (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signaling consists of three steps: a heptahelical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein that dissociates into an alpha subunit bound to GTP and beta and gamma subunits after interaction with the ligand-bound receptor, and an effector (in this case, adenylyl cyclase) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP). The topology of adenylyl cyclase is characterized by two tandem repeats of six hydrophobic transmembrane domains separated by a large cytoplasmic loop and terminates in a large intracellular tail. Generation of cAMP follows receptor-linked activation of the heteromeric G-protein (G_s) and interaction of the free $G_{\alpha s}$-chain with the adenylyl cyclase catalyst. Protein kinase A (PKA) and possibly the exchange factor directly activated by cAMP (EPAC) are the target of the generated cAMP. In the long term, vasopressin also increases aquaporin-2 (AQP2) expression via phosphorylation of the cAMP responsive element binding protein (CREB), which stimulates transcription from the AQP2 promoter. Cytoplasmic vesicles carrying the water channel proteins (represented as homotetrameric complexes) are fused to the luminal membrane in response to AVP, thereby increasing the water permeability of this membrane. Microtubules and actin filaments are necessary for vesicle movement toward the membrane. The mechanisms underlying docking and fusion of AQP2-bearing vesicles are not known. The detection of the small GTP-binding protein Rab3a, synaptobrevin 2 and syntaxin 4 in principal cells suggests that these proteins are involved in AQP2 trafficking [20]. When AVP is not available, water channels are retrieved by an endocytic process, and water permeability returns to its original low rate. Internalized AQP2 can either be targeted to recycling pathways or to degradation via lysosomes. AQP3 and AQP4 water channels are expressed on the basolateral membrane. The importance of an endoplasmic reticulum calcium sensor for vasopressin/aquaporin signaling is also represented with coupling between STIM1 and Orai1 during calcium depletion possibly induced by AQP2 signaling [17].

osmolalities are then tested every 30 min over the next 4 h. Other affected family members should also be tested and blood samples be obtained for DNA testing with appropriate consent. Wong *et al.* [1] also used a haplotype analysis with known polymorphic sequences close to the *AVPR2* gene, which was demonstrated to be a strong indication for the subsequent identification of an *AVPR2* mutation. We prefer a sequencing approach of the suspected gene(s), particularly in polyuric infants.

There is, however, a rare possibility that in a family with hereditary central [16] or nephrogenic diabetes insipidus, DNA sequencing will not identify a disease-causing mutation in the known genes responsible for polyuric disorders, including secondary hereditary diabetes insipidus [17]. A disease-causing splicing variant with some conservation of wild splicing resulting in a mild phenotype has recently been identified in *AVPR2* [18]. Also, a recent autosomal recessive stromal interactive molecule (*Stim1*) mutation responsible for a partial NDI in stroke-prone spontaneously hypertensive-A3 (SHR-A3) rats demonstrates the importance of an endoplasmic reticulum calcium sensor for vasopressin/aquaporin signaling [19] (Figure 1). The phenotype observed in SHR-A3 rats is mild with basal urine osmolalities around 500 mmol/kg with corresponding plasma osmolalities of 303 mmol/kg and a urine osmolality of 2300 mmol/kg after 24 h of dehydration. It is unlikely that the loss of function of this gene will result in a severe phenotype in humans. Finally, there is great hope to use the CRISPR (clustered regularly interspaced short palindromic repeats) gene editing technology to correct monogenic disorders, but 'off-target' sites are feared and it is too early to predict the human use of this promising tool [21].

Conflict of interest statement

None declared.

(See related article by Wong *et al.* Persistent severe polyuria after renal transplant. *Clin Kidney J* (2016) 9: 180–183.)

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