GENETICS IN ENDOCRINOLOGY

Pathophysiology, diagnosis and treatment of familial nephrogenic diabetes insipidus

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Abstract

For an endocrinologist, nephrogenic diabetes insipidus (NDI) is an end-organ disease, that is the antidiuretic hormone, arginine-vasopressin (AVP) is normally produced but not recognized by the kidney with an inability to concentrate urine despite elevated plasma concentrations of AVP. Polyuria with hyposthenuria and polydipsia are the cardinal clinical manifestations of the disease. For a geneticist, hereditary NDI is a rare disease with a prevalence of five per million males secondary to loss of function of the vasopressin V2 receptor, an X-linked gene, or loss of function of the water channel AQP2. These are small genes, easily sequenced, with a number of both recurrent and private mutations described as disease causing. Other inherited disorders with mild, moderate or severe inability to concentrate urine include Bartter's syndrome and cystinosis. *MAGED2* mutations are responsible for a transient form of Bartter's syndrome with severe polyhydramnios. The purpose of this review is to describe classical phenotype findings that will help physicians to identify early, before dehydration episodes with hypernatremia, patients with familial NDI. A number of patients are still diagnosed late with repeated dehydration episodes and large dilations of the urinary tract leading to a flow obstructive nephropathy with progressive deterioration of glomerular function. Families with ancestral X-linked *AVPR2* mutations could be reconstructed and all female heterozygote patients identified with subsequent perinatal genetic testing to recognize affected males within 2 weeks of birth. Prevention of dehydration episodes is of critical importance in early life and beyond and decreasing solute intake will diminish total urine output.

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Invited Author's profile

Daniel G Bichet, MD is Professor of Medicine, Pharmacology and Physiology at the Université de Montréal and a staff nephrologist at the Hôpital du Sacré-Coeur de Montréal. In collaboration with Mariel Birnbaumer (Baylor) his laboratory identified the first mutations responsible for X-linked nephrogenic diabetes insipidus. Dr. Bichet obtained a Canadian Institute Health Research Chair in Genetics of Renal Diseases from 2003 to 2010. His laboratory is contributing to the prevention of extreme dehydration states in children with polyuric disorders. Dr. Bichet received the Medal of the Kidney Foundation of Canada in 1998, a Doctorat Honoris Causa from the University of Nancy (France) in 1999 and the Jean Hamburger Medal in 2010.

Pathophysiology and etiologies of familial NDI

Water reabsorption in principal cells of the collecting duct: two critical proteins: the vasopressin V2 receptor and the aquaporin water channel

Approximately 180 L of primary glomerular filtrate is produced every day by healthy kidneys.

The vast majority of this filtrate is reabsorbed in the proximal tubule, which is freely permeable to water owing to the constitutive expression of aquaporin-1 (AQP1) water channels (1). As solutes are reabsorbed in the proximal tubule, water follows passively along the osmotic gradient. The remaining urine is thus still isotonic when it enters the loop of Henle, the key segment for counter-current concentration (Fig. 1).

Further removal of sodium chloride occurs in the distal convoluted tubule via SLC12A3 (also known as Na⁺-Cl⁻ cotransporter, NCC, thiazide inhibited, transporting one sodium and one chloride). At entry into the AVP-sensitive connecting tubules and collecting ducts, urine osmolality is typically around 50–100 mosmol/kg. The final osmolality of the urine is solely dependent on the availability of water channels. If these channels are present, water exits the tubule following the interstitial concentration gradient and the urine is concentrated. If no water channels are present dilute urine will be excreted (Fig. 2).

AVPR2 is a G-protein-coupled receptor (GPCR) with loss-of-function (NDI) and gain-of-function, the nephrogenic syndrome of inappropriate antidiuresis (NSIAD)

The AVP-AVPR2-AQP2 shuttle pathway

Water homeostasis in the kidney is regulated by three key proteins. AVP, secreted from the posterior pituitary (2), activates the process of water reabsorption by binding to the vasopressin V2 receptor (AVPR2) (Fig. 2) located on the basolateral membrane of collecting duct cells. The final step in the antidiuretic action of AVP is the exocytic insertion of a specific water channel, aquaporin-2 (AQP2), into the luminal membrane, thereby increasing the water permeability of that membrane. These water channels are members of a superfamily of integral membrane proteins that facilitate water transport (3, 4). AQP2 is the vasopressin-regulated water channel in renal collecting ducts. It is exclusively present in principal cells of inner medullary collecting duct cells and is diffusely distributed

in the cytoplasm in the euhydrated condition, whereas apical staining of AQP2 is intensified in the dehydrated condition or after vasopressin administration. These observations are thought to represent the exocytic insertion of preformed water channels from intracellular vesicles into the apical plasma membrane (the shuttle hypothesis) (Fig. 2).

The short-term regulation of AQP2 by AVP involves the movement of AQP2 from the intracellular vesicles to the luminal membrane, and in the long-term regulation, which requires a sustained elevation of circulating AVP for 24 h or more, AVP increases the abundance of water channels. This increase is thought to be a consequence of increased transcription of the AQP2 gene (5). AQP3 and AQP4 are the water channels in basolateral membranes of renal medullary collecting ducts. In addition, vasopressin increases the water reabsorptive capacity of the kidney by regulating the urea transporter UT-A1, which is expressed in the inner medullary collecting duct, predominantly in its terminal part (6). AVP also increases the permeability of principal collecting duct cells to sodium (7). In summary, in the absence of AVP stimulation, collecting duct epithelia exhibit very low permeabilities to sodium, urea, and water. These specialized permeability properties permit the excretion of large volumes of hypotonic urine formed during intervals of water diuresis. In contrast, AVP stimulation of the principal cells of the collecting ducts leads to selective increases in the permeabilities of the apical membrane to water (Pf), urea (PUrea), and sodium (PNa).

Loss of function or gain of function of AVPR2

Clinically significant impairment of signal transduction generally requires loss of function of both alleles of a gene encoding a G-protein-coupled receptor; thus, most such diseases are autosomal recessive (8), but there are several exceptions including X-linked NDI and the X-linked nephrogenic syndrome of inappropriate antidiuresis (NSIAD). NDI is the mirror image of NSIAD with four identified AVPR2 gain-of-function mutations (Fig. 3): R137C, R137L, F229V, I130N (9, 10, 11). In NDI, the kidneys cannot concentrate the urine, whereas in NSIAD urinary dilution is impaired, independent of the presence or absence of vasopressin. Consequently, patients with NDI are at risk of hypernatremic dehydration, whereas hyponatremia is a typical manifestation of NSIAD, mimicking the syndrome of inappropriate antidiuresis (SIADH) (12). The diagnostic pathways also mirror: In NDI an agonist for the vasopressin V2 receptor (AVPR2),

Figure 1

Schematic representation of the renal concentration and dilution mechanisms. The loop of Henle forms a counter-current multiplier system that concentrates the urine. Urine is isotonic when it enters the loop of Henle and hypotonic when it exits into the collecting duct. The concentration gradient generated in the loop of Henle is driven by the active reabsorption of NaCl in the thick ascending limb by the transporter solute carrier family 12 member 1 (SLC12A1, also known as NKCC2, a sodium, potassium, chloride co-transporter). The mechanism of concentration in the thin descending limb is not completely resolved, but likely involves passive water efflux and/or NaCl influx. Final concentration of urine occurs in the collecting duct and depends on the availability of aquaporin 2 water channels. The osmolalities of the tubular fluid and interstitial fluid are indicated. Urine concentration begins in the thin descending limb (TDL). Mechanisms of concentration include AQP1-mediated exit of water into the medullary interstitium. Aqp1 expression is mainly restricted to the first 60% of the TDL rather than the deeper papillary parts in which the steepest part of the osmotic gradient is generated (57). Urine subsequently enters the thick ascending limb (TAL, also known as the diluting segment), which is impermeable to water, due to the lack of expression of any aquaporin, but actively removes sodium chloride via NKCC2, thereby diluting the urine. This electroneutral protein co-transporters one sodium, one potassium and two chlorides, hence the abbreviation NKCC2 (one of the C is for Co-transport), is inhibited by furosemide (58). This NKCC2 co-transporter is responsible for 10–25% of the total sodium reabsorption of the nephron and a ROMK channel recycles more than 90% of the reabsorbed potassium in the lumen, while sodium is reabsorbed at the luminal membrane by the Na-K-ATPase and chloride returns to the interstitial fluid through the chloride channels CIC-Ka and -Kb (right part of Fig. 1). Loss-of-function of NKCC2, ROMK or CIC-Kb or Barttin will be responsible for Bartter's syndrome from type 1 to 4 with loss of water associated with variable solutes (vide infra). The MAGED2 protein is expressed in the TAL and in the distal convoluted tubule increasing both the expression of NKCC2 and the sodium co-transporter NCC (59). The accumulation of solutes in the interstitium generates the driving force for the removal of water from the thin descending limb (TDL) (in long-looped nephrons) and the entry of sodium chloride (in short-looped nephrons), completing the counter-current multiplier.

such as d-amino D-arginine vasopressin (dDAVP), is given to assess the ability of the kidneys to concentrate urine. Conversely, administration of an AVPR2 antagonist, such as tolvaptan provides an assessment of urinary dilution capacity in patients suspected of NSIAD. In patients who

did not present with dysnatremia, yet, are suspected of having an underlying defect in urinary concentration, a water deprivation (NDI) or water load (NSIAD) challenges the kidneys for an appropriate response. Lastly, vasopressin levels, measured either directly or indirectly via

Figure 2

Schematic representation of the effect of arginine vasopressin to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V_2 receptor, AVPR2 (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signaling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein that dissociates into 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 6) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase 6 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 inter-action 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. On the long term, vasopressin also increases 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, see assembly of AQP2 homtetrameric complexes further on in the discussion of AQP2 mutants) 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 stimulation of adenylyl cyclase by the β_3 adrenergic receptor and other GPCRs known to be expressed in principal cells and the stimulation of AQP2 expression through the frizzled d8- β -catenin pathway are also represented.

Figure 3

Schematic representation of the V2 receptor (AVPR2) and identification of 193 putative disease-causing loss-of-function AVPR2 mutations and 5 gain-of-function AVPR2 mutations. Predicted amino acids are shown as their one-letter amino acid codes. A solid symbol indicates a codon with a missense or nonsense mutation; a number (within a triangle) indicates a different mutation on the cDNA level affecting the same codon; other types of mutations are not indicated on the figure. There are 95 missense, 18 nonsense, 46 frameshift deletion or insertion, 7 in-frame deletion or insertion, 4 splice-site, and 22 large deletion mutations, and one complex mutation. The five gain-of-function AVPR2 mutations are R137C, R137L, F229V, I130N.

copeptin (13), can help distinguish nephrogenic disorders of urinary concentration from those of disturbed vasopressin secretion (13).

Germline-derived gain-of-function variants of Gs alpha-coding GNAS gene identified in nephrogenic syndrome of inappropriate antidiuresis

Two recent studies have identified mutations in the stimulatory Gs alpha-protein GNAS as another cause of NSIAD. Miyado *et al.* (14) reported two families with a dominantly inherited form of NSIAD segregating with the GNAS variants p.F68_G70 del and p.M255V. The Gas mutation p.F376V was reported in two unrelated patients with hyponatremia, and it was associated with additional clinical symptoms, suggesting gain of function not only of AVPR2 but also of other GPCRs, including the lutropin (LHGR) and parathyroid hormone (PTH1R) receptors (15). The severity of the phenotype in the patients with the dominantly inherited mutations was quite variable: some patients presented with seizures in early childhood associated with euvolemic hyponatremia, inappropriately elevated urine osmolality, and suppressed vasopressin levels. Other patients had no apparent symptoms and were normonatremic when investigated, but they had elevated urine osmolality despite suppressed vasopressin levels and a history of spontaneously low fluid intake.

Symptomatic family members were treated with fluid restriction with normalization of hyponatremia.

Clinical presentation and history of X-linked NDI (OMIM #304800)

X-linked NDI is secondary to AVPR2 mutations, which result in a loss of function or dysregulation of the V2 receptor (16). Male patients bearing AVPR2 mutation have a phenotype characterized by early dehydration episodes, hypernatremia, and hyperthermia as early as the first week of life. Hypernatremia with an inappropriately low urine osmolality could be observed on the first day of life (DGB personal observations). Dehydration episodes can be so severe that they lower arterial blood pressure to a degree that is not sufficient to sustain adequate oxygenation to the brain, kidneys, and other organs. Mental and physical retardation and renal failure are the classic 'historical' consequences of a late diagnosis and lack of treatment. Heterozygous female patients may exhibit variable degrees of polyuria and polydipsia because of skewed X chromosome inactivation and we have observed two AVPR2 heterozygous females with severe dehydration hypernatremic episodes. Mental retardation, a consequence of repeated episodes of dehydration, was prevalent in the Crawford and Bode study, which found that only 9 of 82 patients (11%) had normal intelligence (17).

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Among the 143 Japanese patients with congenital NDI (90% bearing AVPR2 mutations), 20 patients (14%) had mental retardation (18). The Nijmegen group demonstrated that the majority of their patients with NDI have normal intelligence (19).

Early recognition and treatment of X-linked NDI with an abundant intake of water allows a normal life span with normal physical and mental development (20) and we know affected male members of the Hopewell pedigree (vide infra) living past 80 years of age. Two characteristics suggestive of X-linked NDI are the familial occurrence and the confinement of mental retardation to male patients. We therefore assume that the family described in 1892 by McIlraith and discussed by Reeves and Andreoli was a family with X-linked NDI (21, 22). Lacombe and Weil described a familial form of diabetes insipidus with autosomal transmission and without any associated mental retardation (23). The descendants of the family originally described by Weil were later found to have neurohypophyseal autosomal dominant familial neurohypophyseal (adFNDI) (OMIM #192340) (24). Patients with adFNDI retain some limited capacity to secrete AVP during severe dehydration, and the polyuro-polydipsic symptoms usually appear after the first year of life, when the infant's demand for water is more likely to be understood by adults.

The first manifestations of X-linked NDI can be recognized during the first week of life. The infants are irritable, cry almost constantly, and although eager to suck, will vomit milk soon after ingestion unless pre-fed with water. The history given by the mothers often includes persistent constipation, erratic unexplained fever, and failure to gain weight. Even though the patients characteristically show no visible evidence of perspiration, increased water loss during fever or in warm weather exaggerates the symptoms. Unless the condition is recognized early, children experience frequent bouts of hypertonic dehydration, sometimes complicated by convulsions or death. Mental retardation is a common consequence of these episodes. The intake of large quantities of water, combined with the patient's voluntary restriction of dietary salt and protein intake, lead to hypocaloric dwarfism beginning in infancy. Affected children frequently have lower urinary tract dilation and obstruction, probably secondary to the large volume of urine produced. Dilation of the lower urinary tract is also seen in patients with primary polydipsia and in patients with neurogenic diabetes insipidus (25, 26). Chronic renal insufficiency may occur by the end of the first decade of life and could be the result of episodes of

dehydration with thrombosis of the glomerular tufts. Chronic kidney disease later in life is likely secondary to urological complications as a result of flow obstructive nephropathy: 43% of the 173 NDI Japanese patients had urological complications and 6% had renal failure (18).

Thirty-one years ago we observed that the administration of desmopressin, a V2 receptor agonist, caused an increase in plasma cAMP concentrations in normal subjects, but had no effect in 14 male patients with X-linked NDI (27). Intermediate responses were seen in obligate carriers of the disease, possibly corresponding to half of the normal receptor response. On the basis of these results, we predicted that the defective gene in these patients with X-linked NDI was likely to code for a defective V2 receptor (27). X-linked NDI is a rare disease, with an estimated prevalence of approximately 8.8 per million male live births in the province of Quebec (Canada) (28). In defined regions of North America, the prevalence is much higher. Our group estimated the incidence in Nova Scotia and New Brunswick (Canada) to be 58 per million male live births because of shared ancestry (29).

An additional example has been identified in a Mormon pedigree whose members reside in Utah (Utah families). This pedigree was originally described by Cannon (29). The 'Utah mutation' is a nonsense mutation (L312X) predictive of a receptor that lacks transmembrane domain 7 and the intracellular COOH terminus (29).

The largest known kindred with X-linked NDI is the Hopewell family, named after the Irish ship Hopewell, which arrived in Halifax, Nova Scotia, in 1761. Aboard the ship were members of the Ulster Scot clan, descendants of Scottish Presbyterians who migrated to Ulster province in Ireland in the seventeenth century and left Ireland for the New World in the eighteenth century. Although families arriving with the first emigration wave settled in northern Massachusetts in 1718, the members of a second emigration wave, passengers of the Hopewell, settled in Colchester County, Nova Scotia. According to the 'Hopewell hypothesis', (30) most patients with NDI in North America are progeny of female carriers of the second emigration wave. This assumption is based mainly on the high prevalence of NDI among descendants of the Ulster Scots residing in Nova Scotia. In two villages with a total of 2500 inhabitants, 30 patients have been diagnosed, and the carrier frequency has been estimated at 6%.

Given the numerous mutations found in North American X-linked NDI families, the Hopewell hypothesis cannot be upheld in its originally proposed form. However,

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among X-linked NDI patients in North America, the W71X mutation (the Hopewell mutation) is more common than the other AVPR2 mutation. It is a null mutation (W71X), predictive of an extremely truncated receptor consisting of the extracellular NH2-terminus, the first transmembrane domain, and the NH2-terminal half of the first intracellular loop. Because the original carrier cannot be identified, it is not clear whether the Hopewell mutation was brought to North America by Hopewell passengers or by other Ulster Scot immigrants. We found other families from Nova-Scotia bearing the Hopewell mutation and definitely arriving in Nova-Scotia before the Hopewell ship and linked to the Hopewell pedigree (31). The diversity of AVPR2 mutations found in many ethnic groups (whites, Japanese, African Americans, and Africans), and the low frequency of the disease are consistent with an X-linked recessive disease that in the past was lethal for male patients and was balanced by recurrent mutations. In X-linked NDI, loss of mutant alleles from the population occurs because of the higher mortality of affected male patients compared with healthy male patients, whereas gain of mutant alleles occurs by mutation. If affected male patients with a rare X-linked recessive disease do not reproduce and if mutation rates are equal in mothers and fathers, then, at genetic equilibrium, one-third of new cases in affected male patients will be caused by new mutations. Our group has described ancestral mutations, *de novo* mutations, and potential mechanisms of mutagenesis. These data are reminiscent of those obtained from patients with late-onset autosomal dominant retinitis pigmentosa. In one-fourth of patients, the disease is caused by mutations in the light receptor rhodopsin. Here, too, many different mutations (approximately 100) spread throughout the coding region of the rhodopsin gene have been found (32).

The basis of loss of function or dysregulation of 28 different mutant V2 receptors (including nonsense, frameshift, deletion, and missense mutations) has been studied with the use of *in vitro* expression systems. Most of the mutant V2 receptors tested were not transported to the cell membrane and were retained within the intracellular compartment. Our group also demonstrated that misfolded AVPR2 mutants could be rescued *in vitro* but also *in vivo* by nonpeptide vasopressin antagonists acting as pharmacologic chaperones (33, 34). This new therapeutic approach could be applied to the treatment of several hereditary diseases resulting from errors in protein folding and kinesis (35).

The AVPR2 mutations (D85N, V88M, R104C, R106C, Y128S, L161P, G201D, T273M, F287L, M311V, N317K,

N317S, N321Y, P322S and the splice mutant c.276A>G) have been associated with a mild phenotype and some of these patients bearing these mutations have been successfully treated with dDAVP (18, 36, 37, 38, 39) (Fig. 3).

Clinical presentation and history of autosomal recessive and autosomal dominant NDI secondary to loss of function of AQP2 (OMIM #107777)

The AQP2 gene is located on chromosome region 12q12-q13. Approximately 10% of NDI cases are caused by autosomal mutations in AQP2. When we receive a new family with NDI, we always sequence the AVPR2 gene first except if there is father to son transmission, suggesting an autosomal dominant inheritance (AQP2 dominant) or polyhydramnios during pregnancy suggesting Bartter's or MAGDE2 mutations. Forty-eight mutations and a large deletion have been reported, which are either autosomal recessive (34 mutations reported) or autosomal dominant (8 mutations reported) (40, 41). Both male and female patients who are affected with congenital NDI have been described as homozygous for a mutation in the AQP2 gene or carry two different mutations (Fig. 4). The clinical severity of dehydration phenotypes is similar for patients with loss of function of AQP2 as compared to patients with loss of function of AVPR2. The difference is the severity of signs and symptoms of polyuria, polydipsia, dehydration episodes, observed in female patients homozygous or compound-heterozygous for an AQP2 mutation(s) as compared to female heterozygous for an AVPR2 mutation. Adult women with recessive mutation in AQP2 are also at risk of hypernatremic dehydration if they vomit during early pregnancy and, like all the patients with NDI, should never receive intravenous isotonic saline (*vide infra*). Experimental structures are not yet available for AVPR2 but numerous structures are available for aquaporins including AQP2 (42, 43). For AQP2, six trans-membrane helices surround a narrow water-conducting channel. In the membrane, four aquaporin molecules are assembled to form a homotetramer (Fig. 4). Each monomer exhibits two conserved Asn-Pro-Ala (NPA) sequence motifs, which lie in the middle of the permeation channel, forming a constriction. Another constriction, known as the aromatic/Arg (ar/R) selectivity filter, is located at the extracellular side of the channel. The C-terminal tail is 45 residues long in AQP2 which allows AQP2 interaction and post-translational modifications sites, including phosphorylation sites. Well-diffracting crystals of the full-

Figure 4

A representation of the AQP2 protein and identification of 48 putative disease-causing AQP2 mutations. A monomer is represented with six transmembrane helices. The location of the PKA phosphorylation site (Pa) is indicated. The extracellular, transmembrane and cytoplasmic domains are defined according to Deen *et al.* (60). Solid symbols indicate the location of the mutations and triangles are indicating aminoacids with more than one mutation in the same codon (for references, see Table 1 of (40): M1I; L22V; V24A; L28P; G29S; A47V; Q57P; G64R; N68S; A70D; V71M; R85X; Q93X; G100X; G100V; G100R; I107D; 369delC; T125M; T126M; A147T; D150E; V168M; G175R; G180S; C181W; P185A; R187C; R187H; A190T; G196D; W202C; G215C; S216P; S216F; Asn220Thr; K228E; R254Q; R254L; E258K and P262L. GenBank accession numbers – AQP2: AF147092, Exon 1; AF147093, Exons 2 through 4. NPA motifs and the N-glycosylation site are also indicated).

length AQPs are difficult to obtain, therefore, the available AQP2 experimental structures are truncated and do not include the N- and C-terminal tails. Calvanese *et al.* (43) identified AQP2 mutations affecting (1) the pore, (2) the tetramer assembly, (3) the monomer folding, and (4) signal loss for the protein phosphorylation. Mutations affecting the monomer folding by altering the intra-monomer helices packing cause the most severe phenotypes. These mutants are non-functional with no water passage under osmotic gradient observed, since unfolded and therefore retained in the endoplasmic reticulum. The functionality of mutants whose pore signature motifs – NPA boxes and the ar/R selectivity filter – are affected is also compromised. However, mutations affecting other features of the pore, such as its dimension and composition, or the tetramer assembly are associated with milder phenotypes, with resulting mutants partially retaining their water channel functionality (43).

Autosomal dominant mutations are believed to be restricted to the carboxy-terminal end of the AQP2 protein and to operate through a dominant negative effect whereby the mutant protein associates with functional

AQP2 proteins within intracellular stores, thus preventing normal targeting and function (44).

Other hereditary polyuro-polydipsic syndromes

Polyuria, polydipsia, electrolyte imbalance, and dehydration in cystinosis

Polyuria may be as mild as persistent enuresis or as severe as to contribute to death from dehydration and electrolyte abnormalities in infants with cystinosis who have acute gastroenteritis (45).

Polyuria in hereditary hypokalemic salt-losing tubulopathies

Patients with polyhydramnios, hypercalciuria, and isosthenuria have been found to bear *KCNJ1* (ROMK), *SLC12A1* (NKCC2) and *MAGED2* mutations. Patients with polyhydramnios, profound polyuria, hyponatremia,

hypochloremia, metabolic alkalosis, and sensorineural deafness were found to bear BSND mutations. These studies demonstrate the critical importance of the proteins ROMK, NKCC2, and Barttin in transferring NaCl to the medullary interstitium and thereby generating, together with urea, a hypertonic milieu (46) (Fig. 1 right part).

Carrier detection, perinatal testing and treatment

We encourage physicians who observe families with X-linked and autosomal recessive diabetes insipidus to recommend mutation analysis or cell-free fetal DNA analysis (47, 48) before the birth of an infant because early diagnosis and treatment can avert the physical and mental retardation associated with episodes of dehydration. Diagnosis of X-linked NDI was accomplished by mutation testing of cultured amniotic cells or chorionic villus samples ($n=17$) or cord blood obtained at birth ($n=75$) in 92 of our patients from 79 families. Thirty-nine male patients were found to bear mutant sequences; 28 males had normal sequences. Diagnosis of AQP2 autosomal recessive mutants was done in 4 families for a total of 6 subjects, 3 were found to be homozygous for the previously identified mutation, 2 were heterozygous, and 1 had a normal sequence on both alleles. The affected patients were immediately treated with abundant water intake, a low-sodium diet, and hydrochlorothiazide. They never experienced episodes of dehydration, and their physical and mental development is normal. Gene analysis is also important for the identification of nonobligatory female carriers in families with X-linked NDI. Most female patients heterozygous for a mutation in the V2 receptor do not present with clinical symptoms, and a few are severely affected (28) and Bichet, unpublished observations. Mutational analysis of polyuric patients with cystinosis, hypokalemic salt-losing tubulopathy, nephronophthisis, and apparent mineralocorticoid excess is also of importance for definitive molecular diagnosis (49).

All complications of congenital NDI are preventable by an adequate water intake. Thus, patients should be provided with unrestricted amounts of water from birth to ensure normal development. In addition to a low-sodium diet, the use of diuretics (thiazides, 3 mg/kg/day, usually 25 mg bid in young adults, with amiloride 0.3 mg/kg/day to prevent hypokalemia) or indomethacin (2 mg/kg/day) may reduce urinary output. This advantageous effect must be weighed against the side effects of these

drugs (thiazides: electrolyte disturbances; indomethacin: reduction of the GFR and gastrointestinal symptoms). Crawford and Kennedy observed that the chronic administration of thiazide to animals with pituitary diabetes insipidus, and to patients with pituitary or nephrogenic diabetes insipidus, results in a striking diminution in urinary volume as well as an increased urinary osmolality (50). Earley and Orloff gave thiazides with a low sodium diet to four male patients from 7–17 years of age with NDI likely bearing *AVPR2* mutations and observed an increase in urine osmolality and a decrease in urine volume (Fig. 5) (51). The antidiuresis results from mild sodium depletion induced by the inhibition of thiazide-sensitive co-transporter SLC12A3 in the distal tubule. The loss of sodium leads to a reduction in plasma volume with subsequent enhanced proximal reabsorption of the glomerular filtrate, so that less water is presented to the collecting duct and lost in the urine. In hereditary NDI, there is a maximal low urine osmolality determined by the loss of *AVPR2* function and the urine osmotic load and the urine volume will be less diluted by an increase proximal reabsorption, hence, an increased in urine

Figure 5

Graphical representation of the effect of sodium intake on recovery from antidiuresis induced by hydrochlorothiazide in patient SZ with X-linked nephrogenic diabetes insipidus studied by Earley and Orloff (51). (1): control measurements during 3 days with a sodium intake of 50 mEq/24 h; (2) hydrochlorothiazide 25 mg every 8 h during 6 days with a sodium intake of 50 mEq/24 h; (3) hydrochlorothiazide 25 mg every 8 h during 4 days with a sodium intake of 9 mEq/24 h; (4) hydrochlorothiazide discontinued during 4 days with a sodium intake of 9 mEq/24 h; (5) hydrochlorothiazide discontinued during 2 days with a sodium intake of 100 mEq/24 hours on day 1 and 50 mEq/24 h on day 2. Please note the increase in urine osmolality from 100 to 150 mosmol/kg for the time period 2, 3 and 4.

osmolality after thiazide administration and low sodium intake. The thiazide effect is not due to a unique property of the thiazide derivatives since it was also observed with a mercurial diuretic likely inducing the same extracellular volume contraction. A possible inhibition of carbonic anhydrase by thiazide might be involved (52).

Inhibitors of prostaglandin synthesis are prescribed in the first years of life when management is the most complicated. The effect of these drugs can be quite marked when first initiated and hyponatraemic seizures associated with rapid lowering of plasma sodium levels as a result of commencing indomethacin and hydrochlorothiazide have been reported (53). Many affected infants frequently vomit because of an exacerbation of physiologic gastroesophageal reflux. These young patients often improve with the absorption of an H₂ blocker and with metoclopramide (which could induce extrapyramidal symptoms) or with domperidone, which seems to be better tolerated and efficacious. Bypassing the vasopressin V2R signalling has been tested experimentally but no proof-of-concept clinical studies have been done (16). The intravenous administration of saline solutions is strictly forbidden in patients with NDI since water is excreted and saline retained with dangerous, potentially lethal, augmentations of plasma sodium (54).

Water deprivation tests and copeptin measurements in familial NDI

A dehydration test is often not indicated in patients with hereditary NDI since data obtained from the hospital chart will document a plasma sodium higher than 145 mEq/L with a concomitant urine osmolality less than 200 mmol/kg H₂O. Further, a dehydration test is dangerous since, due to the high urine hypo-osmotic loss, severe hypernatremia could occur with intracerebral bleeding secondary to dehydration. Water restriction is not performed in newborns or very young infants suspected to have hereditary nephrogenic DI (e.g. documented plasma sodium 145 mEq/L or higher with a concomitant urine osmolality ≤200 mosmol/kg). If the diagnosis is unclear in such patients, the preferred diagnostic test is the administration of desmopressin (1 µg subcutaneously or intravenously infused over 20 min, maximum dose 0.4 µg/kg of body weight) with measurement of the urine osmolality at baseline and at 30-min intervals over the next 2 h. If the urine osmolality does not increase by more than 100 mosmol/kg over baseline, the diagnosis of nephrogenic DI is made and DNA should be obtained for mutation analysis (55).

Water deprivation tests for older infants and children should be performed in the hospital under close medical supervision. The patient should not be allowed to lose more than 5% of their body weight. Monitoring of vital signs (temperature, pulse, and blood pressure), body weight, laboratory tests, urine and plasma osmolalities, and the plasma sodium concentration are essential.

Plasma copeptin measurements are high in familial NDI, that is higher than 21.4 pg/mL (56) reflecting a normal vasopressin response to dehydration. These measurements are not necessary to confirm the diagnosis based on the absent urine osmolality response to dDAVP.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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