Acquired Nephrogenic Diabetes Insipidus

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Nephrogenic diabetes insipidus (NDI) is defined as the inability of the kidney to concentrate urine owing to the insensitivity of the distal nephron to the antidiuretic hormone, arginine vasopressin. NDI can be either a congenital or an acquired disorder. Acquired NDI most commonly is secondary to drugs such as lithium or metabolic disturbances, such as hypokalemia and hypercalcemia. Disturbance of the aquaporin-2 shuttle is the underlying molecular basis of acquired NDI. NDI is diagnosed with the help of a water-deprivation test. Patients with the disorder will have a urinary osmolality of less than 300 mosm/kg H₂O despite water deprivation. On administration of aqueous vasopressin, patients with NDI will show little or no increase in urine osmolality. Therapy consists of identifying and correcting the underlying disorder, or withdrawing the offending drug. Other treatment options that may be beneficial include diuretics, nonsteroidal anti-inflammatory drugs, decreased dietary solute intake, and desmopressin (DDAVP).

This report reviews NDI and discusses the following: (1) physiology of the aquaporin 2 shuttle, (2) diagnostic criteria, (3) causes, and (4) management of the disease.

Physiology of the Aquaporin 2 Shuttle

The understanding of the molecular mechanisms of acquired nephrogenic disease has been enhanced greatly by the seminal work of Agre et al. The expression of aquaporin 1 (AQP1) in Xenopus laevis oocytes by Preston et al explained how water crosses biological membranes. Since then, at least 7 aquaporins have been discovered in the kidney. AQP2 has been shown to be the primary target for vasopressin regulation of collecting duct water permeability. The underlying urinary concentrating defect in acquired forms of NDI results either from decreased expression of AQP2 or from impaired delivery of these channels to the apical plasma membrane.

In the following section I will attempt to explain the salient features of the AQP2 shuttle and how its disturbance leads to acquired NDI (Fig 1). The antidiuretic hormone vasopressin (AVP) is released from the posterior pituitary in response to an increase in plasma osmolality or a decrease in circulating volume. AVP then acts on the kidney to increase water reabsorption from the collecting ducts. AVP mediates this effect by binding to vasopressin type-2 receptors on the basolateral surface of...
principal cells stimulating the protein Gs, which activates adenyl cyclase. This leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn activates protein kinase A (PKA). This activation of PKA leads to phosphorylation of AQP2 at Ser 256. This phosphorylation is essential for AQP2 translocation from intracellular storage vesicles to the apical membrane, which causes an increase in water permeability of renal principal cells.

The AQP2-bearing vesicles are translocated from their intracellular location to an apical location along the microtubular network. Dynein, a minus end-directed motor protein that has been isolated in the kidney, along with dynactin, a protein complex that mediates the interaction of dynein with vesicles, associates with AQP2-bearing vesicles.

A reorganization of the actin cytoskeleton also has been shown to be essential in the trafficking of AQP2. It is possible that in the unstimulated cell, the actin cytoskeleton anchors the AQP2-bearing vesicles. Vasopressin depolymerizes the apical F-actin in rat inner medullary collecting ducts, resulting in the fusion of water channel–carrying vesicles with the apical membrane.

Thus, it appears that the delivery of AQP2-bearing vesicles to the apical plasma membrane is dependent on the microtubular network of the cell. The subsequent fusion of the AQP2-bearing vesicles to the plasma membrane then is directed by interaction of specific proteins on the vesicles (vSNAREs) with specific proteins on the plasma membrane (tSNAREs).

The AQP2, which now has docked and fused at the plasma membrane, subsequently is recycled by an endocytic process. AQP2 first accumulates in clathrin-coated pits and then is internalized via a clathrin-mediated process that is stimulated on removal of antidiuretic hormone from the membrane.

**Diagnosis of Nephrogenic Diabetes Insipidus**

The principal issue in a polyuric patient is to sort out the causes of polyuria-primary polydipsia and central and nephrogenic DI. The two most useful tests for the diagnosis are the plasma sodium concentration and the water-restriction test.

**Plasma Sodium Concentration**

A sodium concentration of less than 137 mEq/L is indicative of primary polydipsia. In diabetes insipidus, a high-normal plasma sodium level of more than 142 mEq/L usually is seen. True hypernatremia with a plasma sodium level of more than 150 mEq/L typically is not seen in DI because the initial loss of water stimulates the thirst mechanism, resulting in an increase in intake to match the urinary losses. An exception to this rule may occur with a central lesion, impairing thirst and leading to plasma sodium concentrations exceeding 160 mEq/L.

**Water-Deprivation Test**

Water intake is restricted until 3 consecutive hourly specimens show urine osmolality within 10% of each other or the plasma osmolality reaches 295 mosmol/kg. Aqueous vasopressin (5 U subcutaneously) is given and urinary osmolality is measured after 60 minutes. Patients with NDI will have a urinary osmolality after water deprivation of less than 300 to 500 mOsm/kg H2O. This is in contrast to individuals with primary polydipsia in whom urinary osmolality will exceed 500 mOsm/kg H2O.

To further distinguish nephrogenic from central causes of
Table 1 Causes of Acquired NDI

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<tr>
<th>Class</th>
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DI, plasma vasopressin is measured after dehydration. In NDI, plasma vasopressin will exceed 5 ng/L, whereas in central diabetes insipidus (CDI), plasma vasopressin will be undetectable or markedly reduced. Finally, on administration of exogenous vasopressin, patients with CDI will show an increase in urinary osmolality, and those with NDI will show little or no increase.19

**Causes of Acquired NDI**

**Lithium**

Lithium is a commonly used mood-stabilizing agent with 1 in 1,000 Americans receiving the drug (Table 1).20 Approximately 20% to 30% of these patients will develop polyuria owing to a vasopressin-resistant urinary concentrating defect (ie, NDI).21 Animal studies have examined the effects of oral lithium treatment on rats for 25 days.22 AQP2 and AQP3 levels were found to be reduced in animals on lithium to approximately 5% of levels seen in control animals.22 This downregulation of AQP2 expression was paralleled by the development of severe polyuria. Immunoelectron microscopy of AQP2 labeling in the inner medullary collecting duct principal cells showed a reduction in AQP2 in the apical plasma membrane and in the basolateral plasma membrane and intracellular vesicles.23 The reduction in AQP2 expression may be caused by a lithium-induced impairment in the production of cAMP in collecting duct principal cells.24 This is consistent with the presence of a CAMP-responsive element in the 5’-untranslated region of the AQP2 gene and the demonstration that mice with inherently low cAMP levels have low expression of AQP2.25 In addition, after cessation of lithium therapy, there is a very slow recovery in AQP2 expression and restoration of urinary concentration, consistent with clinical findings.23

**Hypokalemia**

The molecular defects underlying development of NDI in hypokalemia have been studied in well-established animal models.26 When rats are maintained on a potassium-deficient diet for 11 days, there is significant down regulation of AQP2 expression in both the inner medulla and cortex of kidneys in these animals. This downregulation though, is significantly less than that seen in lithium-treated rats. A moderate increase in urine production parallels this downregulation in AQP2 expression. Subsequently, when these rats are maintained on a normal potassium diet for 7 days, there is normalization of both AQP2 levels and of urinary concentrating capacity.

**Hypercalcemia**

Similar to hypokalemia another electrolyte disorder, hypercalcemia, also is associated with the development of NDI. An experimental model of vitamin D–induced hypercalcemia has been used to study the molecular defects underlying the NDI seen in this disorder.27 Rats treated orally for 7 days with dihydrotachysterol showed a 3-fold increase in urine production, along with a 50% reduction in urine osmolality. Consistent with this, immunoblotting of membrane fractions showed a 50% reduction in AQP2 expression in kidney inner medulla from hypercalcemic rats. Wang et al28 have elucidated the molecular mechanism of this disorder further. They showed that in addition to downregulation of collecting duct AQP2 expression, there was also a significant downregulation of the bumetanide-sensitive Na-K-2Cl cotransporter BSC-1 in membranes from inner the stripe of the outer medulla. This defect in the thick ascending limb may participate in the development of the urinary concentrating defect.

**NDI Caused By Urinary Tract Obstruction**

AQP2 expression levels have been studied in a rat model of bilateral reversible ureteral obstruction.29 After bilateral obstruction for 24 hours, AQP2 expression levels are reduced markedly. Because during the obstruction period urine production is zero, this result supports the view that diuresis per se is not the cause of decreased AQP2 levels.

After release of the obstruction there is marked polyuria along with an increased solute-free water clearance. Even after normalization of urine output at 7 days, the animals continue to have an impaired urinary concentrating defect in response to 24 hours of thirsting. AQP2 levels continue to be suppressed to 50% of normal at this point of time.

Further experiments were performed to examine whether this reduction in AQP2 expression in bilateral ureteral obstruction was caused by local factors (increased tissue pressure and changes in renal hemodynamics) or by systemic changes in the animal. On studying the effects of unilateral ureteral obstruction for 24 hours, there was a profound (23% of control) downregulation of AQP2 in the obstructed kidney and a moderate (75% of control) downregulation in the nonobstructed kidney.30 These results support the view that local factors play an important role in AQP2 downregulation in the obstructed kidney, but the signals leading to this decrease...
remain unknown. However, in the nonobstructed kidney systemic factors are predominant. These potentially may involve decreased circulating vasopressin or washout of metabolites from the obstructed kidney or may be a consequence of renorenal nerve activity, known to play a role in the compensation for unilateral obstruction.31

Management
Management of acquired NDI primarily consists of identifying and correcting the underlying disorder or withdrawing the offending drug. In most instances this is sufficient to reverse the disorder and relieve the polyuria. However, in patients with long-standing tubular damage (eg, long-term lithium use), the condition may be irreversible.32 In such patients, there are several treatment options that may be beneficial.

Diuretics
Thiazide diuretics remain the mainstay of treatment of NDI. They reduce polyuria by a combination of mild volume depletion that induces an increase in proximal sodium and water reabsorption and a direct increase in water permeability in the inner medullary collecting duct.33 Amiloride can be used in combination with thiazides for its additive effect on the antipolyuric response.34

In addition, amiloride has a particular role in reversible lithium toxicity owing to its site and mechanism of action. The drug closes the sodium channels in the luminal membrane of the collecting tubule cells. These channels are the means by which filtered lithium enters the cell and interferes with its response to antidiuretic hormone (ADH).35

Nonsteroidal Anti-Inflammatory Drugs
Treatment with nonsteroidal anti-inflammatory drugs has been advocated for emergent or resistant cases of drug-induced NDI because of its prompt effect on polyuria.36 The efficacy of these drugs is dependent on the inhibition of renal prostaglandin synthesis. This has the effect of increasing concentrating ability because prostaglandins normally antagonize the action of ADH.37

Decreased Dietary Solute Intake
Dietary modification using a low-salt, low-protein diet can help diminish the urine output in nephrogenic DI.18 This occurs because the decrease in net solute excretion (as sodium salts and urea) will reduce the urine output at a given urine osmolality.

DDAVP
Most patients with nephrogenic DI have partial rather than complete resistance to ADH. Achieving a supraphysiologic hormone level therefore can increase the renal effect of ADH to a level that is relevant clinically.38

In conclusion, it is my opinion that with the increasing recognition that prolonged exposure to offending agents very often can lead to irreversible disease, early recognition and removal of the agent assumes paramount importance. This should be supplemented with close monitoring, correction of electrolyte levels, and administration of diuretics, nonsteroidal anti-inflammatory drugs, and demopressin (DDAVP) as needed.

References