SEMINARS IN
NEPHROLOGY

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 H_2O 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).
Semin Nephrol 26:244-248

KEYWORDS **Nephrogenic diabetes insipidus, aquaporin 2, vasopressin resistance, lithium, hypokalemia, hypercalcemia**

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. The majority of patients who have a mild version of the disorder compensate for fluid losses with increase water intake. In severe cases, however, uncompensated symptoms can develop such as marked dehydration, neurologic symptoms, and encephalopathy.[1] In addition, when the underlying cause of the disorder is drug-induced, the risk for severe drug intoxication is markedly increased owing to dehydration and consequent renal failure.[2]

NDI can be either a congenital or an acquired disorder. Acquired NDI most commonly is secondary to drugs or metabolic disturbances.[3] The earlier concept of acquired NDI as a benign disorder, easily reversed by withdrawal of the offending agent, has come under increased scrutiny and revision in recent years.[4] Current knowledge of the disorder emphasizes chronic irreversible changes with prolonged exposure.[5] This awareness has made early recognition of acquired NDI an even more important topic for the clinician.

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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.[6] The expression of aquaporin 1 (AQP1) in *Xenopus laevis* oocytes by Preston et al[6] explained how water crosses biological membranes. Since then, at least 7 aquaporins have been discovered in the kidney.[7] Of these, AQP2 has been shown to be the primary target for vasopressin regulation of collecting duct water permeability.[7] 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.[8]

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.[9] AVP mediates this effect by binding to vasopressin type-2 receptors on the basolateral surface of

 0270-9295/06/$-see front matter
doi:10.1016/j.semnephrol.2006.03.004

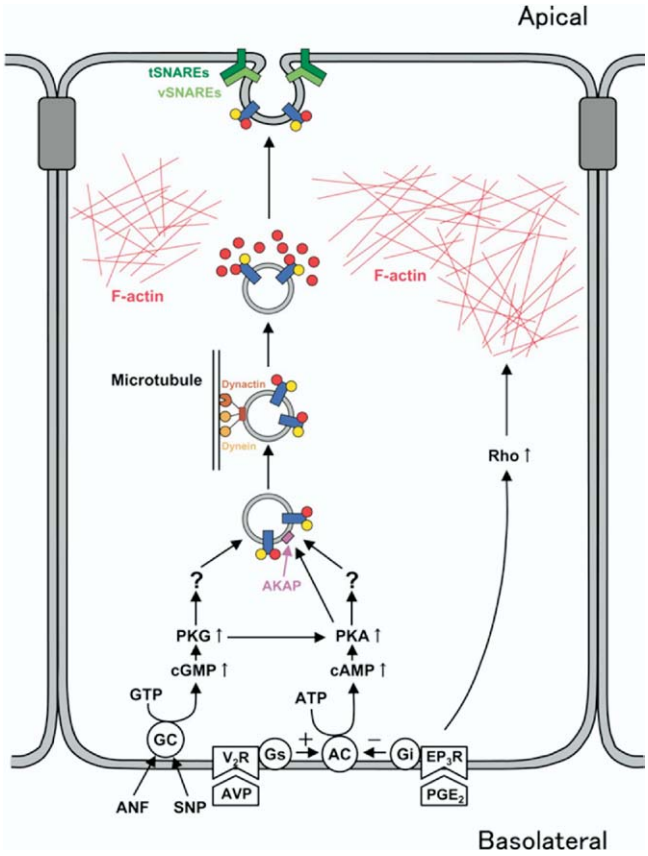

Figure 1 Representation of the postulated molecular mechanisms for regulation of AQP2 trafficking. Binding of AVP to its receptor (vasopressin type-2 receptor) activates adenylate cyclase (AC) via the G protein, G_s. This then increases cAMP levels and induces PKA-mediated phosphorylation of AQP2 that is necessary for AQP2 sorting to the apical membrane. Alternatively, stimulation of prostaglandin E_3 receptor (EP_3R) by prostaglandin E_2 (PGE_2) inhibits AC via the G-protein, G_i. In addition, EP_3R activates Rho, which promotes the formation of F-actin. F-actin polymerization functions as a barrier for AQP2 trafficking. cGMP-PKG pathway stimulated by sodium nitropruside (SNP) or atrial natriuretic factor (ANF) via guanylate cyclase (GC) also induces AQP2 sorting. Microtubule-associated motor proteins, including dynein and dynactin, are involved in AQP2 trafficking. AQP2 binds to SPA-1 and G-actin. It is speculated that SPA-1 binding to AQP2 reduces the levels of Rap1GTP that may trigger F-actin disassembly in a restricted area around AQP2, resulting in the promotion of the AQP2 sorting. The targeting, docking, and fusion of AQP2-containing vesicles with the apical membrane involves the interaction of vesicle soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (v-SNAREs) and target membrane soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (t-SNAREs). Reprinted with permission from Noda.[39]

principal cells stimulating the protein G_s, which activates adenyl cyclase.[10] 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.[11] 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.[12]

The AQP2-bearing vesicles are translocated from their intracellular location to an apical location along the microtubular network.[13] 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.[14]

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.[15]

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).[16]

The AQP2, which now has docked and fused at the plasma membrane, subsequently is recycled by an endocytotic 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.[17]

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.[18]

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 H_2O. This is in contrast to individuals with primary polydipsia in whom urinary osmolality will exceed 500 mOsm/kg H_2O.

To further distinguish nephrogenic from central causes of

Table 1 Causes of Acquired NDI

Renal causes	**Acute renal failure in diuretic phase**
	Chronic renal failure
	Postobstructive diuresis
Systemic causes	**Sickle cell disease or trait**
	Amyloidosis
	Sarcoidosis
	Sjogren's syndrome
	Hyperthyroidism
Electrolyte disorders	**Hypercalcemia**
	Hypokalemia
Drugs	**Lithium**
	Amphotericin B
	Demeclocycline
	Cidofovir
	Foscarnet
	Ifosfamide
	Ofloxacin
	Orlistat
	Colchicine
	Contrast agents

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 al[28] 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

1. Adam P: Evaluation and management of diabetes insipidus. Am Fam Physician 55:2146-2153, 1997
2. Bendz H, Aurell M, Lanke J: A historical cohort study of kidney damage in long-term lithium patients. Continued surveillance needed. Eur Psychiatry 16:99-206, 2001
3. Garofeanu CG, Weir M, Rosas-Arellano MP, et al: Causes of reversible nephrogenic diabetes insipidus: A systematic review. Am J Kidney Dis 45:626-637, 2005
4. Thompson CG, France AJ, Bayliss PH: Persistent nephrogenic diabetes insipidus following lithium therapy. Scott Med J 42:16-17, 1997
5. Bendz H, Sjodin I, Aurell M: Renal function on and off lithium in patients treated with lithium for 5 years or more. A controlled, prospective lithium-withdrawal study. Nephrol Dial Transplant 11:457-460, 1996
6. Agre P, Preston GM, Smith BL, et al: Aquaporin CHIP: the archetypal molecular water channel. Am J Physiol Renal Fluid Electrolyte Physiol 265:F463-F476, 1993
7. Nielson S, Froklaer J, Marples D, et al: Aquaporins in the kidney: From molecules to medicine. Physiol Rev 82:205-244, 2002
8. Marples D, Frokiaer J, Knepper MA, et al: Disordered water channel expression and distribution in acquired nephrogenic diabetes insipidus. Proc Assoc Am Physicians 110:401-406, 1998
9. Knepper MA, Neilsen S, Chou CL, et al: Mechanism of vasopressin action in the renal collecting duct. Semin Nephrol 14:302-321, 1994
10. Edwards RM, Jackson BM, Dousa TP: ADH-sensitive cAMP system in papillary collecting duct: effect of osmolality and PGE2. Am J Physiol 240:F311-F318, 1981
11. Katsura T, Gustafson CE, Ausiello DA, et al: Protein kinase A phosphorylation is involved in regulated exocytosis of aquaporin 2 in transfected LLC-PK1 cells. Am J Physiol 272:F817-F822, 1997
12. Fushimi K, Sasaki S, Marumo F: Phosphorylation of serine 256 is required for cAMP-dependent regulatory exocytosis of the aquaporin 2 water channel. J Biol Chem 272:14800-14804, 1997
13. Valenti G, Hugon JS, Bourguet J: To what extent is microtubular network involved in antidiuretic response? Am J Physiol 255:F1098-F1106, 1988
14. Marples D, Schroer TA, Ahrens N, et al: Dynein and dynacatin colocalize with AQP2 water channels in intracellular vesicles from kidney collecting duct. Am J Physiol 274:F384-F394, 1998
15. Simon H, Gao Y, Franki N, et al: Vasopressin depolymerizes apical F-actin in rat inner medullary collecting duct. Am J Physiol 265:C757-C762, 1993
16. Franki N, Macaluso F, Gao Y, et al: Vesicle fusion proteins in rat inner medullary collecting duct and amphibian bladder. Am J Physiol 268: C792-C797, 1995
17. Strange K, Willingham MC, Handler JS, et al: Apical membrane endocytosis via coated pits is stimulated by removal of antidiuretic hormone from isolated, perfused rabbit cortical collecting tubule. J Membr Biol 103:17-28, 1988
18. Rose BD, Post TW: Clinical Physiology of Acid-Base and Electrolyte Disorders (ed 5). New York, McGraw-Hill, 2001, pp 148-757, 767-772
19. Lanese D, Teitelbaum I: Hypernatremia, in Jacobson HR, Stricker GE, Klahr S (eds): The Principles and Practice of Nephrology (ed 2). St. Louis, Mosby, 1995, pp 893
20. Peet M, Pratt JP: Lithium current status in psychiatric disorders. Drugs 46:7-17, 1993
21. Boton R, Gaviria M, Batlle DC: Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium. Lithium therapy. Am J Kidney Dis 10:329-345, 1987
22. Kwon TH, Laursen UH, Marples D, et al: Altered expression of renal

aquaporins and Na transporters in rats with lithium-induced nephrogenic diabetes insipidus. Am J Physiol 279:F552-F564, 2000
23. Marples D, Christensen S, Christensen EI, et al: Lithium induced downregulation of aquaporin-2 water channel expression in rat kidney medulla. J Clin Invest 95:1838-1845, 1995
24. Christensen S, Kusano E, Yusufi AN, et al: Pathogenesis of nephrogenic diabetes insipidus due to chronic administration of lithium in rats. J Clin Invest 75:1869-1879, 1985
25. Matsumura Y, Uchida S, Rai T, et al: Transcriptional regulation of aquaporin-2 water channel gene by cAMP. J Am Soc Nephrol 8:861-867, 1997
26. Marples D, Frokiaer J, Dorup J, et al: Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. J Clin Invest 97:1960-1968, 1996
27. Earm JH, Christensen BM, Frokiaer J, et al: Decreased aquaporin-2 expression and apical plasma membrane delivery in kidney collecting ducts of polyuric hypercalcemic rats. J Am Soc Nephrol 9:2181-2193, 1998
28. Wang W, Kwon TH, Li C, et al: Reduced expression of Na-K-2Cl cotransporter in medullary thick ascending limbs in vitamin D-induced hypercalcemia in rat. Am J Physiol 282:F34-F44, 2002
29. Frokiaer J, Marples D, Knepper MA, et al: Bilateral ureteral obstruction downregulates expression of vasopressin-sensitive AQP2 water channel in rat kidney. Am J Physiol 270:F657-F668, 1996
30. Frokiaer J, Christensen BM, Marples D, et al: Downregulation of aquaporin-2 parallels changes in renal water excretion in unilateral ureteral obstruction. Am J Physiol 273:F213-F223, 1997
31. Nielsen S, Frokiaer J, Marples D, et al: Aquaporins in the kidney: From molecules to medicine. Physiol Rev 82:205-244, 2002
32. Bendz H: Kidney function in a selected lithium population. A prospective, controlled, lithium-withdrawal study. Acta Psychiatr Scand 72: 451-463, 1985
33. Earley LE, Orloff J: The mechanism of antidiuresis associated with the administration of hydrochlorothiazide to patients with vasopressin-resistant diabetes insipidus. J Clin Invest 41:1988, 1962
34. Knoers N, Monnens LAH: Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. J Pediatr 117:499-502, 1990
35. Batlle DC, Von Riotte AB, Gaviria M, et al: Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 312:408, 1985
36. Lam SS, Kjellstrand C: Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. Ren Fail 19: 183-188, 1997
37. Stokes JB: Integrated actions of renal medullary prostaglandins in the control water excretion. Am J Physiol 240:F471, 1981
38. Miller M, Kalkos T, Moses AM, et al: Recognition of partial defects in antidiuretic hormone secretion. Ann Intern Med 73:721, 1970
39. Noda Y, Sasaki S: Trafficking mechanism of water channel aquaporin-2. Biol Cell 97:885-892, 2005