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CASE REPORT

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Nephrolithiasis complicating treatment of diabetes insipidus

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Abstract A decrease in urine volume is considered the therapeutic goal of the treatment of central diabetes insipidus (DI) with desmopressin (dDAVP). A low urine volume is a risk factor for kidney stone formation. This is the first report of nephrolithiasis in association with DI. It is likely that successful therapy with dDAVP and the patient's own purposeful decreased fluid intake contributed to calcium oxalate stone formation. Prevention of stone recurrence requires an increase in urine volume. The patient's compliance with this recommendation led to an episode of acute hyponatremia, a well-known complication of dDAVP therapy. The challenge of the management of stones in the setting of DI requires balancing the conflicting goals of both decreasing and increasing urine volume.

Keywords Calcium oxalate · Desmopressin · dDAVP · Hyponatremia · Polyuria · Urinary calculi/drug therapy · Water-electrolyte imbalance

Introduction

The treatment of central diabetes insipidus (DI) is intended to limit urine flow rates, polyuria and polydipsia. Low urine volume is an important risk factor for kidney stone formation. One might expect, therefore, that nephrolithiasis would be at least an occasional complication of successful therapy of DI with desmopressin. To our knowledge, until this case report, kidney stones have not previously been described as a complication of treated DI or in association with DI. Our patient's condition was further complicated because prevention of recurrent nephrolithiasis entails prescription of an increased fluid intake in order to maintain higher urine volumes. In a patient with both nephrolithiasis and DI, the challenge in management is that the treatment strategies for the two conditions are in conflict. Following her presentation with kidney stones, our patient's course included a hospitalization for acute hyponatremia.

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Case presentation

A 35-year-old woman presented for evaluation of nephrolithiasis. At the age of 9 years, the patient developed polyuria, polydipsia and blurry vision. She was noted to have atrophy of the posterior pituitary gland on a computerized tomogram (CT) of the head. With no evidence of a tumor, infiltrative disease or vascular lesion, the patient was deemed to have idiopathic central diabetes insipidus. Successful therapy with nasal insufflation of the synthetic vasopressin analog 1-deamino-8-D-arginine-vasopressin (dDAVP) was initiated. Her dose varied but for many years as an adult she took 0.05 ml (5 μg) three times each day.

The patient successfully limited her urine output so that she could, without difficulty, attend college and law school. At age 32 she had an episode of renal colic. She was found to have radio-opaque calculi bilaterally. She underwent successful extracorporeal shock wave lithotripsy (ESWL) of an obstructing ureteral stone. Stone analysis showed 100% calcium oxalate monohydrate. The patient was instructed by her urologist to increase her fluid intake and thereby her urine output.

Her past medical history was otherwise unremarkable. She worked as an attorney. The patient had no family history of renal stones or DI. Her father had recently developed end stage renal disease of unknown etiology and required hemodialysis.

At 4 months after ESWL, the patient developed confusion and disorientation. She was seen in an emergency department with lethargy attributed to hyponatremia. The physical exam revealed a well developed woman with a blood pressure of 132/78 without orthostasis and a pulse of 68 beats/min. Respiratory, cardiovascular, and abdominal examinations were unremarkable and other than her disorientation, her neurologic exam was non-focal. Serum chemistry testing demonstrated sodium 120 mEq/l, potassium 4.4 mEq/l, chloride 83 mEq/l, bicarbonate 19 mEq/l, glucose 94 mg/dl, blood urea nitrogen 5 mg/dl, calcium 8.8 mg/dl, phosphate 2.9 mg/dl, magnesium 1.6 mg/dl, creatinine 0.6 mg/dl, albumin 4.5 g/dl, plasma osmolality 233 mOsm/kg H_2O. Complete blood count was normal, including hemoglobin 14.8 g/dl. Urine chemistry concentrations included sodium 8 mEq/l and potassium 4 mEq/l. Urine output was not recorded. Urinalysis showed specific gravity 1.007, pH 7.0; urine osmolality was not ordered. Plain radiograph of the abdomen showed several 1–2 mm calcifications of the kidneys bilaterally.

The dDAVP was discontinued and normal saline was given intravenously at a rate of 150 ml/h. After 8 h the patient's serum sodium concentration was 125 mEq/l, and at 11 h 140 mEq/l. The dDAVP was restarted at a lower dose of 0.025 ml (2.5 μg) three times a day and the patient was discharged.

One year later, she sought counseling regarding stone prevention. Two 24 h collections of urine were obtained on the patient's usual diet and dDAVP regimen. The results are presented in Table 1. The patient had relatively minimal urinary risk factors for stone formation with mild hyperoxaluria and normal calcium, citrate and uric acid excretion. Urine volume was 1.7 l. Serum intact parathyroid hormone level was normal at 52 pg/ml. Serum bicarbonate concentration, which was low at the time of the episode of hyponatremia, was normal on all subsequent determinations. Abdominal radiographs, ultrasound and nephrotomograms were indicative of calcific, non-obstructing radio-opacities bilaterally within the renal collecting systems. She was advised to maintain the lower dose of dDAVP but to use it less frequently. She was also instructed to maintain a higher urine volume than she had in the past and reduce dietary oxalate intake, though she had no clear history of significant dietary oxalate ingestion. Most doses of dDAVP are now taken as needed, self-administered when urine volume increases. Because of her concern about the new regimen, she was also given potassium bicarbonate 25 mEq/day in order to increase urinary citrate excretion.

In the 5 years since her episode of hyponatremia, the patient has had no growth of her existing stones, and no development of new stones as judged by serial ultrasounds. Follow-up urine collections (Table 1, "post-consultation") demonstrate higher urine volumes, with lower supersaturation of calcium oxalate. Urinary citrate and pH are higher with no change in supersaturation of calcium phosphate. Oxalate excretion is slightly reduced. She has always had normal serum sodium concentrations; her most recent value was 140 mEq/l.

Table 1 Results of 24 h urine collections before consultation in the Stone Prevention Program and afterwards. Post-consultation values represent the mean of three samples taken over 4 years. CaOx, calcium oxalate; CaP, calcium phosphate; normal values (in parentheses) provided by Litholink (Chicago Ill.)

24 h urine	Mean results of two samples pre-consultation	Mean results of three samples post consultation
Volume (l/d) (0.5–4)	1.7	2.3
Creatinine (mg/d)	1090.5	1137
Urine pH (5.8–6.2)	6.67	7.07
Uric acid (g/d) (women < 0.75)	0.55	0.62
Citrate (mg/d) (women > 550)	661	814
Calcium (md/d) (women < 200)	175.5	196.0
Calcium (mg/kg body weight) (< 4.0)	2.9	3.2
Oxalate (mg/d) (20–40)	42.0	37.7
Phosphate (g/d) (0.6–1.2)	0.62	0.74
Sodium (mM/d) (50–150)	107	149
Potassium (mM/d) (20–100)	54	84
Magnesium (mg/d) (30–120)	92	84
Supersaturation CaOx (6–10)	8.0	4.8
Supersaturation CaP (0.5–2)	1.6	1.5
Supersaturation uric acid (0–1)	0.2	0.1

Discussion

We are not aware of a previous report of co-existing nephrolithiasis and DI. Since the goal of therapy of DI is to prevent polyuria, one might expect that successful therapy with dDAVP and limitation of water intake would result in an increase in urinary supersaturation of stone-forming calcium salts and an increased risk of stone formation. Since this association has not been described previously, it may be the case that most patients, despite therapy with dDAVP, maintain relatively high urine volumes resulting in relatively low urinary supersaturation of calcium oxalate. In the case of the patient we present here, symptomatic kidney stones developed during therapy for DI. We cannot state that the therapy of DI was the sole cause of stone formation, since we do not have a measure of urine volume or an estimate of urinary supersaturation of calcium salts prior to the onset of renal colic. However, based on the patient's history, we would expect that treatment with dDAVP and her purposeful limit of fluid intake would

have further increased the supersaturation of calcium oxalate.

Urinary risk factors were unremarkable with the exception of the elevated pH, a finding that has no clear explanation. She had no evidence of renal tubular acidosis (the one low serum bicarbonate was most likely due to chronic respiratory alkalosis associated with acute hyponatremia), either the complete or the incomplete form, and she did not have a urinary tract infection. We are unaware of any effect of DI or treatment with dDAVP to affect factors that alter urinary lithogenicity other than urine volume.

Patients with nephrolithiasis are commonly advised to increase their fluid intake to prevent recurrence of stones [1]. This advice would conflict with the goal of limiting polyuria in patients with DI. In this case, after many years of uncomplicated therapy of DI, the patient developed symptomatic hyponatremia 4 months after having ESWL. The patient was told to increase her fluid intake in order to increase her urine output without an adjustment in the dose of dDAVP. It appears that the stone prevention regimen of increased fluid intake caused the patient's hyponatremia. This complication of both acute and chronic use of dDAVP is considered rare but has been associated with seizures [2] and death [3]. Some authorities recommend that dDAVP in the management of DI should be withdrawn once weekly to allow patients to become polyuric and avoid hyponatremia [4].

Although stones have not previously been reported in human cases of DI, bladder stones have been described in Brattleboro rats, which are homozygous for functional vasopressin deficiency and central diabetes insipidus [5]. Urine from these rats is undersaturated with respect to apatite and struvite crystal phases but in the presence of chronic urinary tract infection with *Proteus* sp. these rats form apatite and struvite bladder stones. Our patient did not have a urinary tract infection.

We are not able to find studies detailing what ranges or mean values for serum sodium concentration and urine volume are achieved in otherwise normal adults with chronic central DI. A recent study demonstrated a high frequency of hypernatremic readings in children with central DI and with either abnormal thirst mechanisms or physical disabilities leading to impaired access to water [6]. These children must otherwise be at low risk for stones with reduced solute excretion, or stones would be expected to occur. That paper is also notable for describing home measurements of serum sodium concentration, a technique that could significantly improve decision making regarding fluid therapy in patients with DI or at risk for stones.

dDAVP is also used chronically in the management of enuresis and von Willebrand disease [7]. Stone formation, which might be expected as a complication seen with chronic use, has not previously been ascribed to dDAVP in either of these settings. Minor and infrequent side effects of dDAVP include headache, flushing, nausea, tachycardia, vertigo, fatigue, and abdominal cramping [7]. Pseudotumor cerebri [8] has been reported in patients using dDAVP chronically for enuresis.

This report is not the appropriate venue to review the proper management of acute hyponatremia. However, we believe that the management in this case led to too rapid and too complete a correction of serum sodium concentration [9]. Administration of normal saline solution is usually not the preferred intravenous therapy in this situation and the dDAVP should have been reinstituted before the patient's serum sodium concentration reached 140 mEq/l. Fortunately, her recovery was uneventful. Measurement of urinary osmolality, not specific gravity, is the preferred method of monitoring urinary dilution and concentration; the specific gravity of 1.007 might represent a spontaneous recovery as the effect of the dDAVP wore off. Interestingly, dDAVP has been used in combination with non-steroidal anti-inflammatory drugs in the treatment of renal colic with mixed success [10]. Such therapy would be inappropriate in a patient with hyponatremia.

Successful long-term management of the patient required that she balance the conflicting demands of her two conditions. Currently, she takes most doses of dDAVP when she notes an increase in urine volume. Her goal, to prevent stone recurrence, is to achieve a urine volume of more than 2 l per day. Obviously this regimen requires a high level of patient compliance and understanding. Were she less intelligent and less capable of understanding the pathophysiology and interactions of her two disorders, the concomitant existence of DI and stones might be even more troublesome than it has been.

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