Case Report

Lithium-Induced Nephrogenic Diabetes Insipidus

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Abstract

We report a case of a 43 year-old female who presented with lithium-induced nephrogenic diabetes insipidus. This patient had history of bipolar disorder for which she had been taking lithium carbonate for last 16 years. Appropriate work up was done and she was diagnosed with nephrogenic diabetes insipidus, secondary to lithium toxicity, and was managed accordingly.

Introduction

Diabetes insipidus is a disorder resulting from deficient anti-diuretic hormone (ADH) action and is characterized by the passage of copious amounts of very dilute urine. This disorder must be differentiated from other polyuric states such as primary polydipsia, osmotic diuresis, and diabetes mellitus.

Nephrogenic diabetes insipidus results when kidneys fail to respond to circulating ADH.

This causes cellular and extra-cellular dehydration, which stimulates thirst and results in polydipsia.[1] As many as 20 to 40 % of patients taking lithium have had symptoms related to a concentrating defect, and 12 percent have frank nephrogenic diabetes insipidus.[2]

Case Report

The presented patient was a 43 year-old female, with a history of bipolar disorder for 16 years and was treated with lithium carbonate 1200 mg per day, risperi-

Table 1.

Serum Na^+	169 mmol/l
Serum K^+	4.6 mmol/l
Serum Cl^-	105 mmol/l
Serum $HCO3^-$	26 mmol/l
Serum Urea	70 mg/dl
Serum Creatinine	2.0 mg/dl
Blood Glucose Random	120 mg/dl
Serum Ca^{++}	8.45 mg /dl
Serum Osmolality	345 mosm/kg
Urine Osmolality	158 mosm/kg
Thyroid Stimulating Hormone	0.74 mu/ml (0.4-4.0 mu/ml)
Serum Lithium	3.2 ng/dl (0.5-1.2 ng/dl)

and carbamazepine. She had symptoms of compulsive water drinking and polyuria since many years. No work up had ever been done for her symptoms prior to this admission. Her past history was significant for essential hypertension, under good control, for three years, and she was taking a combination of furosemide and amiloride.

Patient had recently been admitted to a local hospital for severe pains in both legs. Her hospital course got complicated by diarrhea, drowsiness and aspiration pneumonia. Her condition deteriorated rapidly and she required mechanical ventilation. Tracheostomy was performed. Due to her precarious condition she was transferred to our institution for intensive care and diagnosis. Her investigations on time of arrival were as follows:

On arrival her vitals were as follows: B.P. 80/60, pulse120/min, temperature 100^0F. She was mechanically ventilated, and was drowsy, responding only to deep pain. Her tongue was dry and rest of the examination was unremarkable.

Her urine output varied from 5-11 liters/day. (Her urine osmolality was 158 which dropped to 53 mosm/kg before treatment). Because of persistent hypernatremia and polyuria an endocrine consult was sought. Severe hypernatremia and medical conditions precluded the use of water deprivation test. Initial trial of intravenous desmopressin showed insignificant effect on her urine output. Therefore patient was treated as nephrogenic diabetes insipidus.

As part of her management, lithium carbonate was discontinued. Fluid replacement with 5% dextrose water was started after calculating water deficit, and her mental status improved remarkably. She was allowed to drink as desired. She received combination of indomethacin 50 mg per os every 8 hours and hydrochlorothiazide 50 mg orally every 8 hours. Serum sodium, serum osmolality returned to normal. Maximum urine concentrated to 75 mosm/kg (Table 2). Urine output significantly decreased to 1.8 to 2.5 liters per day and symptom of polydipsia also improved.

Indomethacin was stopped after four weeks of therapy. She was continued on tablets, which were a combina-

Table 2.

Serum Na^+	142 mmol/l
Serum K^+	4.2 mmol/l
Serum Cl^-	102 mmol/l
Serum $HCO3^-$	25 mmol/l
Serum Urea	30 mg/dl
Serum Creatinine	1.24 mg/dl
Serum Osmolality	290 mosmol/kg
Urine Osmolality	75 mosmol/kg

tion of hydrochlorothiazide (25mg) and amiloride (12.5). Initially she was given three tablets/day, which was later, reduced to 2 tablets daily. She did remarkably well, and was discharged from hospital.

Discussion

Nephrogenic diabetes insipidus is caused by renal unresponsiveness to physiologic actions of ADH. Chronic kidney diseases, particularly those affecting medulla and collecting ducts, can cause nephrogenic diabetes insipidus (Figure).

Lithium carbonate reduces the sensitivity of renal tubules to ADH by reducing V2 receptor density or aqua-

Figure. Depicting Osmolality changes in various parts of a nephron.

porin-2 expression.[1,3,4] Lithium impairs the ADH-stimula-

aquaporin-2 expression.[1,3,4] Lithium impairs the ADH-stimulatory effect on adenylate cyclase resulting in less cyclic adenosine monophosphate, which, in turn decreases the water absorption through pores in basolateral membrane of collecting tubules.

Lithium-induced polyuria is partially due to an enhancement of renal prostaglandin action.[5] The cellular mechanism of lithium was investigated by means of indomethacin, an inhibitor of prostaglandin synthesis.[5] It has been observed that long-term treatment of rats with lithium causes a marked decrease in the expression of the aquaporin-2 protein in the medullary collecting duct cells and results in severe nephrogenic diabetes insipidus.[6] Dysregulation of amiloride-sensitive sodium channel (ENaC) may be responsible for increased sodium excretion associated with lithium treatment.[7]

The most recent literature review by Walker et.al summarizes the current view on the persistent irreversible concentrating defect caused by lithium.[8] Patients taking lithium, especially long-term therapy, can develop an irreversible concentrating defect that can persist to varying degrees after lithium is discontinued.

There are three steps to diagnosing nephrogenic diabetes insipidus. First, the physician should take a careful history, perform a physical examination, and order laboratory tests.

The second step is water deprivation test. After baseline urine and serum osmolality and baseline electrolytes are measured, water is withheld for 4-18 hours. Urinary output is measured and patient is weighed before and after fluid deprivation. Serum and urine osmolality and electrolytes are measured again after fluid deprivation. Normal patients have a two-to-four-fold increase in urine osmolality. Third step differentiates between central and nephrogenic diabetes insipidus. Five units of vasopressin are given subcutaneously. One to two hours later serum and urine osmolality is again measured. Patients with central diabetes insipidus would have greater than 50% increase in urine osmolality after vasopressin. Patients with nephrogenic diabetes insipidus would have less than 10% increase in urine osmolality after vasopressin.[1,2]

Diuretic and nonsteroidal anti-inflammatory medications have been used to treat lithium induced nephrogenic diabetes insipidus. There is one case report of ketorolac being used intravenously in an acutely ill patient who failed to respond to indomethacin.[2] In one study, eight cases were described in which nephrogenic diabetes insipidus remained persistent even 57 months after cessation of lithium therapy, and demonstrated a palliative effect of triamterene-hydrochlorothiazide.[9]

References

1. Francis SG, Gardner DG. Basic and clinical endocrinology. 7th ed. New York:McGraw Hill, 2003, pp. 154-8.
2. Kurt AS. Lithium-induced nephrogenic diabetes insipidus. J Am Board Fam Pract 1999;12:43-7.
3. Morello JP, Bichet DG. Nephrogenic diabetes insipidus. Ann Rev Physiol 2001; 63:607-30.
4. Wilson F.William's text book of endocrinology. 8th ed Philadelphia: Saunders, 1992, pp. 339-40.
5. Rapaport J, Chaimovitz C, Alroy GG, Better OS. Lithium induced nephrogenic diabetes insipidus: studies of tubular function and pathogenesis. Isr J Med Sci. 1979;15:765-71.
6. Nine VAMK, Carel HVO. Clinical importance of urinary excretion of aquaporin-2. N Engl J Med 1995;332:1575-6.
7. Jacob N, Tac HK. Segment-specific ENaC downregulation in kidney of rats with lithium-induced NDI. Am J Physiol Renal Physiol 2003;285:1198-209.
8. Walker RG. Lithium nephrotoxicity. Kidney Int Suppl 1993;42:93-8.
9. Guirgius AF, Taylor HC. Nephrogenic diabetes insipidus persisting 57 months after cessation of lithium carbonate therapy. Endocr Pract 2000;6:324-8.