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Persistent nephrogenic diabetes insipidus, tubular proteinuria, aminoaciduria, and parathyroid hormone resistance following longterm lithium administration

William D. Neithercut, Richard J. Spooner, Anne Hendry[1] and John H. Dagg[1]

Departments of Pathological Biochemistry and [1]Medicine, Western Infirmary, Glasgow G11 6NT, UK.

Summary: We report a patient who developed persistent nephrogenic diabetes insipidus associated with renal tubular acidosis, renal resistance to parathyroid hormone, aminoaciduria and proximal tubule pattern proteinuria in the presence of a reduced glomerular filtration rate (19–24 ml/min). A review of the previous reports of persistent nephrogenic diabetes insipidus revealed that in all patients the glomerular filtration rate had been less than 60 ml/min at presentation. Chronic renal failure may therefore predispose to the development of persistent nephrogenic diabetes insipidus in patients receiving lithium.

Introduction

Lithium salts, which are an established treatment of bipolar and some recurrent unipolar affective disorders, have a narrow therapeutic range which makes therapeutic monitoring mandatory.[1-3] Lithium administration has become a common cause of nephrogenic diabetes insipidus.[4-7] In a few patients nephrogenic diabetes insipidus has persisted following the withdrawal of lithium.[8-11] Reduction of glomerular filtration rate has also been attributed to chronic lithium administration although the evidence for this is weak.[7,12] In addition, renal tubular acidosis and tubular proteinuria have also been attributed to chronic lithium administration.[5,7,13-15] We report a patient who developed persistent nephrogenic diabetes insipidus accompanied by chronic renal failure with a renal tubular acidosis and aminoaciduria. We discuss the aetiology of the persistent nephrogenic diabetes insipidus and the other abnormalities of renal tubular function.

Clinical presentation

A 54 year old female with a 33 year history of a bipolar affective illness was referred with a history of 6 weeks of thirst, polyuria, lethargy and a weight loss of 5 kg. Her past medical history included two paracetamol overdoses 4 and 8 years prior to her presentation. Lithium, prescribed under inpatient supervision for 13 of the preceding 16 years, had been stopped 2 weeks after development of thirst and polyuria. Lofepramine, chlorpromazine and orphenadrine were prescribed at the time of presentation.

On examination she was thin, dehydrated, had a flattened affect and psychomotor retardation. Her blood pressure was 122/78 mmHg. The sodium concentration in her serum was 175 mmol/l consistent with hypernatraemic dehydration. Serum and urine osmolalities were 355 mosmol/kg and 129 mosmol/kg respectively.

Examination of fluid balance charts from 3 weeks prior to the development of hypernatraemia showed that she had been polyuric, passing more than 3 litres of urine each day, during the 3 days on which these charts had been kept. Despite unrestricted access to water and complaints of thirst she had been unable to maintain fluid balance.

Initial rehydration was with intravenous 5% dextrose. The sodium concentration in her serum fell to 152 mmol/l within 2 days. Intravenous fluids were discontinued and she was encouraged to take fluids by mouth. Possibly due to a reduced thirst sensation and psychomotor retardation her oral fluid intake was around 2.6 litres/day. Her serum sodium concentration rose over the next 3 days to 182 mmol/l. Intravenous fluids were recommenced with 4 litres of 5% dextrose daily. Following intravenous rehydration and the discontinuation of lofepramine and chlorpromazine her affect and sensation of thirst improved. Her oral fluid intake rose to 4.1–5 litres/day.

Correspondence: W.D. Neithercut, M.R.C.P., M.R.C.Path.
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Investigation

The concentration of lithium in her serum 4 weeks prior to the development of hypernatraemia was 0.81 mmol/l. Lithium administration had been stopped at this time and lithium was not detected in her serum when she presented with hypernatraemia. Over the 13 years preceding the development of nephrogenic diabetes insipidus lithium had been measured on 74 occasions. The lithium concentrations had ranged from 0.53 to 2.4 mmol/l, 11 results were greater than 1.3 mmol/l and 7 were less than 0.7 mmol/l. Acute lithium toxicity had not occurred on any occasion.

To confirm the diagnosis of nephrogenic diabetes insipidus and assess the maximum urine concentration which could be achieved, a water deprivation test was undertaken. Water deprivation was commenced at 22.00 h and continued until 17.00 h the next day. The results in Figure 1 showed that despite a raised basal arginine-vasopressin (AVP) concentration after overnight water deprivation, and an increase in plasma AVP concentration and serum osmolality during the test, no significant change in urine osmolality occurred. An intravenous injection of 2 μg of DDAVP was given at 17.00 h, indicated by an arrow on Figure 1. Only a slight increase in the osmolality of the final urine sample passed that day was observed following this.

As her serum bicarbonate concentration had been persistently low, median 18 mmol/l (range 14–22 mmol/l), and random urine pH measurements were consistently greater than 6.0, an acid load test was undertaken. The results of this (Figure 2) were compatible with a renal tubular acidosis. Her glomerular filtration rate as assessed by 4 consecutive creatinine clearances over a 4-week period was reduced (19–24 ml/min). The 24-hour urine volumes were all greater than 3 litres,

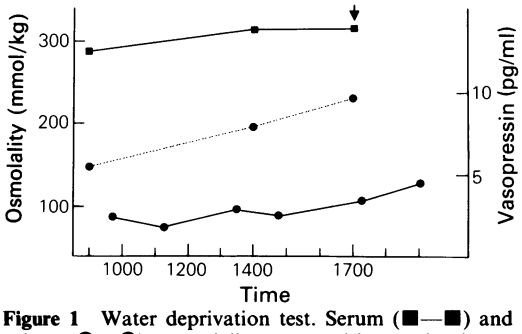

Figure 1 Water deprivation test. Serum (■—■) and urine (●—●) osmolality mosmol/kg and plasma vasopressin (AVP) (●– –●) concentration pg/ml plotted against the time of day during the water deprivation test. At the time indicated by the arrow 2 μg of desmopressin (DDAVP) was administered intravenously.

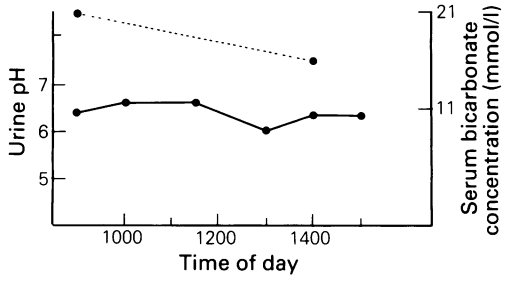

Figure 2 Acid load test (5 g NH_4Cl). Urine pH (●—●) and serum bicarbonate (●– –●) concentration plotted against time of day during a 5 g NH_4Cl acid load test.

ranging from 3.4 to 7.6 litres, confirming that she was polyuric. The 24-hour urine creatinine excretion was low in all collections but was consistently between 4.5 and 4.8 mmol/24 hours despite wide variation in the volumes collected, indicating that these collections were probably complete.

AVP uses cyclic adenosine monophosphate (cAMP) as a second messenger. As parathyroid hormone (PTH) also uses cAMP as a second messenger, an Ellsworth Howard test was conducted.[16] Figure 3 shows that the renal excretion of cAMP in response to the intravenous administration of 200 units of bovine PTH (National Institute of Biological Standards, London, UK) was impaired. The total urinary cAMP excreted during the test was 900 nmol which is less than that found in healthy individuals (range 3100 to 4800 nmol). The basal serum PTH concentration of 42 pmol/l was raised (reference interval 7 pmol/l). The fasting uncuffed calcium concentration was 2.23 mmol/l, the albumin concentration was 41 g/l.

Urine chromatography showed a generalized aminoaciduria which prompted investigation of tubular protein excretion. There was increased excretion of retinol binding protein, 205 μg/mmol creatinine (reference interval 15 μg/mmol creatinine) and *N*-acetyl-glucosaminidase 130 μmol/mmol creatinine (reference interval 35 μmol/mmol creatinine). This was consistent with proximal tubular dysfunction. The total urine protein excretion was less than 0.1 g/24 hours.

Table I shows serial urine and serum osmolalities following investigation. Despite treatment the highest urine osmolality observed during 8 months following diagnosis was 207 mosmol/kg.

A renal ultrasound examination and intravenous urography demonstrated two small functioning kidneys with thinned cortices and slight calyceal clubbing. Histological examination of the kidneys following a post-mortem examination 1 year later revealed changes consistent with an endstage interstitial nephritis.

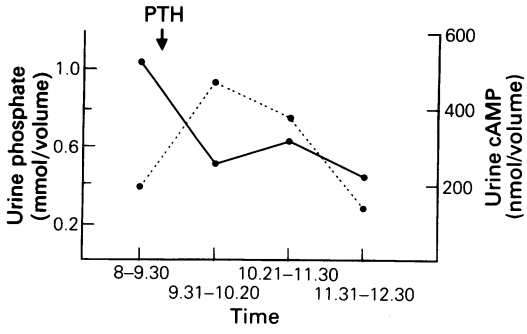

Figure 3 Ellsworth Howard test. Urine phosphate (●—●) mmol/volume and urine cAMP (●– –●) nmol/volume plotted against time of collection during an Ellsworth Howard test. Bovine PTH, 200 units, was administered at the time indicated by the arrow.

Table I Persistence of urine concentrating defect

Days following presentation with hypernatraemia	*Morning urine osmolality (mosmol/kg)*	*Serum osmolality (mosmol/kg)*
0	129	355
28	134	271
35	63	288
63	203	290
99	154	289
117	207	319
145	144	284
180	161	308
208	123	300
236	154	306
250	143	300

Management

Following investigation, treatment was commenced with 5 mg bendrofluazide/day. This failed to reduce her daily urine volumes which remained between 4–9 litres/day. The dose of bendrofluazide was increased to 10 mg/day but without reduction in daily urine volumes. Treatment was then changed to chlorthalidone, initially 200 mg/day reducing to 100 mg/day. On this regimen her serum sodium concentration fell, reaching 114 mmol/l six days after commencement of chlorthalidone. Treatment with chlorthalidone was discontinued and 0.9% saline was given intravenously.

When her serum sodium concentration was again within the reference interval treatment was recommenced with 10 mg bendrofluazide and intranasal desmopressin (DDAVP). However, her serum sodium concentration fell to 120 mmol/l over the next 4 days. It was finally appreciated that her daily fluid intake of 4–5 litres was now in excess of requirement. Her fluid intake was restricted to 2.5 litres/day, DDAVP discontinued and treatment with 5 mg bendrofluazide/day continued. With this treatment regimen her urine output stabilized at 2–3 litres/day. Her serum sodium concentration remained within laboratory reference intervals and her renal function as assessed by serum creatinine concentration did not deteriorate.

She returned to a psychiatric ward 2 months after transfer for investigation. She died 1 year later of bronchopneumonia, and as indicated above, autopsy showed endstage interstitial nephritis.

Discussion

Despite complaining of thirst and having free access to water our patient was unable to maintain an adequate fluid intake prior to treatment, perhaps suggesting that she had a reduced thirst sensation. The thirst mechanism has been found to be intact in patients with cranial diabetes insipidus,[17] although decreased thirst sensation in association with lithium-induced nephrogenic diabetes insipidus has been reported.[18] However, when her affect improved following withdrawal of chlorpromazine and lofepramine, and rehydration she maintained an adequate fluid intake and when treated exhibited a tendency to compulsive water drinking. This suggests that her initial failure to maintain an adequate fluid intake may have been due to a flattened affect and psychomotor retardation.

The mechanism by which lithium causes failure of water reabsorption in the distal tubule is thought to be the impairment of AVP-sensitive adenyl cyclase activity associated with cell membranes.[7,19] This enzyme generates intracellular cAMP which acts as the second messenger for AVP and PTH. Cellular uptake of lithium is thought to be necessary for its inhibitory effect on tubular water reabsorption.[20,21] The intracellular mechanism by which lithium inactivates adenyl cyclase activity, and how this may persist following withdrawal of lithium is not known.

Cellular uptake of lithium is not required for the development of a urinary defect of hydrogen ion excretion.[7] The persistence of this abnormality was consistent with persistent renal structural changes.[22,23] It has been suggested that lithium-induced nephrogenic diabetes insipidus may be associated with tubular cytoplasmic swelling, glycogen deposition, dilation of tubules and microcyst formation.[24,25] These histological changes are reversible but the renal biopsy findings from one patient with persistent nephrogenic diabetes insipidus were consistent with chronic interstitial nephritis.[8] Experimental work has also suggested that chronic tubulo-interstitial changes may occur following long-term treatment with lithium.[23]

At post-mortem examination our patient had an endstage interstitial nephritis. The aminoaciduria, proteinuria, failure of urinary acidification, and renal PTH resistance may, therefore have occurred due to the development of an interstitial nephritis which could have been triggered by lithium administration.

The glomerular filtration rate was found to be less than 70 ml/min in only 15% of patients on long-term lithium.[7] However, in 4 previous reports of persistent nephrogenic diabetes insipidus a reduced creatinine clearance was found, 35–60 ml/min.[8–11] Patients with severe chronic renal failure, GFR less than 14 ml/min, may also develop failure of the urinary concentrating mechanisms, including renal insensitivity to AVP, resulting in the production of hypotonic urine.[26] In addition, patients at risk of developing polyuria are those with higher therapeutic serum concentrations of lithium.[27] As lithium is excreted by the kidney, patients with renal failure may be at risk of higher serum concentrations and greater intracellular accumulation of lithium than those with normal renal function. A reduced glomerular filtration rate may therefore predispose to the development of persistent nephrogenic diabetes insipidus in patients prescribed lithium.

In summary, close monitoring of the GFR of patients treated with lithium may be necessary because a reduced glomerular filtration rate was observed in our patient and in the previous reports of persistent nephrogenic diabetes insipidus.

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