CASE REPORT

Lithium-induced Nephrogenic Diabetes Insipidus

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Abstract

Lithium is a unique agent that remains the gold standard among mood stabilizers. Nephrogenic diabetes insipidus is one of the most common adverse effects as a result of chronic lithium use. However, monitoring is understated and it is often identified by our medical counterparts in an acute setting. We herein report a case of undiagnosed nephrogenic diabetes insipidus in the context of lithium intoxication, brought to attention only following an acute medical condition. As a common medication prescribed by mental health practitioners, early detection of nephrogenic diabetes insipidus should be emphasized as it can lead to increased morbidity and mortality if not promptly identified and managed. Clinicians, especially in the psychiatric setting should actively enquire on the polyuria-polydipsia complex, and remain vigilant in the monitoring of serum sodium, urine output and osmolality.

Keywords: Lithium, Diabetes Insipidus, Toxicity

Introduction

Lithium is a unique agent that remains the gold standard among mood stabilizers. Specific mechanism of action of its mood stabilizing properties remains elusive, but is thought to exert its effects by decreasing glutamate and dopamine while increasing GABA transmission [1]. Despite superior therapeutic properties, a narrow therapeutic range combined with adverse effects prominent on chronic use curtails its use in clinical practice [2]. In the long term, lithium is known to have effects on the endocrine (thyroid and parathyroid glands), renal and neurological system. In the context of the renal system, lithium has been associated with polyuria, nephrogenic diabetes insipidus (NDI), tubulointerstitial nephropathy and renal impairment progressing to end stage renal failure [3].

NDI is one of the most common adverse effects, accounting for 20 – 40 % of patients on chronic lithium use [4]. Despite being a common entity as a result of lithium therapy, it is understated in the psychiatric clinical practice and literature, often identified and reported by our medical counterparts especially in an acute setting. As a common

medication prescribed by mental health practitioners, early detection of NDI should be emphasized as its consequences can be deleterious. We present a case of undiagnosed lithium-induced NDI, in the context of lithium intoxication.

Case report

Mr L is a 50-year-old gentleman with a long history of bipolar I disorder, in full remission, on maintenance therapy of olanzapine 10mg/day, lithium carbonate 1500mg/day and fluphenazine decanoate 50mg monthly. He has no significant past medical history. He presented to the emergency department (ED) with an acute onset of altered mental status, fever, increasing lethargy and poor oral intake of 4 days duration. One week prior, he had diarrhoea which persisted until his presentation to ED.

He has been prescribed lithium carbonate and fluphenazine decanoate for over 20 years with no documented side effects. Relevant laboratory investigations (7 months prior ED) include sodium (Na) 147 mmol/L, urea (Ur) 3.7 mmol/L, creatinine (Cr) 105 umol/L and serum lithium 0.7 mmol/L. Thyroid function test (TFT) was normal.

In ED, Mr L was stuporous with hypertonic limbs and brisk reflexes over bilateral lower limbs. There was no neck stiffness or clonus elicited and no fluctuation in vital signs. An initial investigation revealed leukocytosis (WBC: 18.2), acute kidney injury (AKI) with hypernatremia (Ur 32.3 mmol/L, Cr 360 umol/L, Na 152 mmol/L), raised liver enzymes and creatinine kinase (ALT 89 U/L, ALP 201 U/L, CK 599 (<190 U/L)). Computed tomography of the brain was unremarkable. All psychiatric medications were withheld since admission. Serum lithium on hospital day (HD) 4 found to be 2.54 mmol/L; hence, establishing diagnosis of lithium toxicity secondary to gastrointestinal losses due to AGE and dehydration [7].

The endocrine team conferred a diagnosis of NDI secondary to lithium in view of hypernatremia (170 mmol/L), polyuria, raised serum osmolality (293 – 340 mOsmo/kg) and low urine osmolality (46 – 271 mOsmo/kg). Mr L received intermittent subcutaneous desmopressin and intravenous (IV) fluids for management of NDI. The consultation-liaison (CL) psychiatry team was consulted on HD 11 as he appeared to be restless. A diagnosis of delirium was established, with Mr L exhibiting inattention, disorientation and disorganized thoughts. Delirium was precipitated by lithium toxicity, sepsis, electrolyte imbalance with hypernatremia and transaminitis consistent with laboratory workup of blood culture and sensitivity (C & S) positive for Klebsiella pneumonia, Ur 14.6 mmol/L, Cr 142 umol/L, ALT139 U/L, ALP 229 U/L. Serum Li was 0.11 mmol/L by HD11.

Psychiatric management aimed at balancing the risk of worsening blood parameters against the benefits of commencing an effective medication to manage behavioural changes as well as to attenuate the risk of significant mental deterioration as a result of discontinuation of previous neuroleptics. Mr L was initially started on olanzapine 5mg/day on HD15 after multiple episodes of agitated behaviour. Olanzapine was gradually optimized to 20mg/day whilst closely monitoring his LFTs. Transaminitis and AKI with hypernatremia resolved by HD29 and HD31 respectively. IM fluphenazine 25 mg was introduced at HD34 after Mr L exhibited early relapse symptoms. He was discharged on HD38 and remained in symptomatic remission on his outpatient

visits. Lithium was not recommenced upon resolution of AKI.

Discussion

Within a few weeks of lithium initiation, tubular dysfunction resulting in concentrating defect can occur, manifesting itself as polyuria. Polydipsia associated with lithium is thought to arise from renally mediated polyuria. The polyuria-polydipsia complex has been reported in up to 70 % of patient on chronic lithium [5]. The underlying mechanism behind tubular dysfunction stems from lithium's interference of vasopressin's ability to increase water permeability. Deposition of glycogen in renal tubules through this process leads to tubular dysfunction, progressing to tubule scarring and loss. This may account for the persistence or irreversibility of NDI features long after cessation of chronic lithium use [6]. In essence, NDI is characterized by inadequate renal response to vasopressin with polyuria (urine output of more 3 litres/day in adults) and urine osmolality of less than 300mOsm/kg [7, 8]. Risk factors include duration of treatment, serum lithium levels, frequency of acute intoxication, persistent lithium poisoning, concomitant use of neuroleptics especially antipsychotics [3, 9].

Management of NDI should ideally begin when polyuria emerges, where insult to the kidneys are at its minimal. Strategies include adjusting lithium to the lowest possible dose, single lithium dosing, and avoiding episodes of toxicity by thorough psychoeducation emphasizing on hydration [10]. Acute hypernatremia in the context of lithium-induced NDI require correction of total body water deficits with hypotonic saline. Fluid restriction is not recommended as it can exacerbate hypernatremia. Lithium therapy, especially in the setting of lithium intoxication, should be discontinued [11]. NDI may be reversible upon discontinuation of lithium; however, chronic lithium therapy usually renders NDI irreversible [12]. The time frame of exposure to cessation which constitutes a 'reversible' defect still remains vague [13]. Of particular importance is the risk of severe hypernatremia as a result of persistent concentration defects long after lithium withdrawal [4, 14]. Cessation may not be an option for patients who have tried other neuroleptics and require long term lithium therapy to maintain a stable mental health. Continuation of lithium therapy is, therefore, a challenging decision that requires comprehensive risk benefit analysis. In this subset of patients, amiloride, thiazide diuretics, indomethacin and desmopressin have been demonstrated to be effective remedies [10, 11].

This case demonstrates undiagnosed NDI brought to attention following an acute medical condition. Mr L has history of polyuria, nocturia and polydipsia for many years prior which was only obtained retrospectively following his medical admission. The obscured diagnosis of NDI in line with AGE exacerbated dehydration whilst potentiating lithium toxicity which can be life threatening if not managed promptly [15].

Hansen and Amdisen Classification on Severity of Lithium Toxicity [15]
Grade 1 (mild) Nausea, vomiting, tremor, hyperreflexia, agitation, ataxia, muscle weakness Grade 2 (moderate) Stupor, rigidity, hypertonia, hypotension Grade 3 (severe) Coma, convulsions, myclonia, collapse

In summary, NDI can lead to increased morbidity and mortality if not promptly identified and managed [13]. Clinicians, especially in the psychiatric setting should actively enquire on the polyuria-polydipsia complex, and remain vigilant in monitoring of serum Na, urine output and osmolality. We suggest for timely consultation with the endocrinologist to effectively diagnose and manage lithium-induced NDI, especially in the setting where long term lithium is required.

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Declaration of conflicting interests

The authors have no conflicts of interest to declare.

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