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- hyponatremia
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Lithium (lithium carbonate) toxicity as a cause of nephrogenic diabetes insipidus complicated by acute kidney injury and severe hypernatremia

Lithium is the first-line maintenance therapy in bipolar affective disorder. It is excreted by the kidneys without undergoing metabolism [1]. Several factors can influence its plasma concentration, including sodium levels, fluid intake, and numerous medications, primarily nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics – mainly thiazides – and angiotensin II receptor blockers. Lithium salt toxicity can lead to acute kidney injury and lithium-induced nephrogenic diabetes insipidus (Li-NDI), accompanied by hypernatremic dehydration, which further exacerbates neurological symptoms and can result in patient death [2,3,4]. Chronic lithium therapy may also cause varying degrees of glomerulopathy, predominantly focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD). The article presents two cases of lithium toxicity, the complications that arose during therapy, and the treatment applied. It discusses recommendations regarding the treatment of lithium salt toxicity and the mechanisms leading to acute and chronic nephropathy.

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Introduction

Lithium carbonate remains a cornerstone of long-term prophylaxis for bipolar disorder and is among the longest-used medications in psychiatry. Lithium salt toxicity can cause acute kidney injury and lithium-induced nephrogenic diabetes insipidus (Li-NDI), which may be complicated by hypernatremic dehydration; these sequelae can worsen neurological symptoms and, in severe cases, be fatal [2,3,4]. Lithium is eliminated unchanged by the kidneys [1]. Chronic lithium therapy is also associated with glomerular diseases, most commonly focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD). The principal risk factors are elevated serum lithium concentrations and prolonged duration of treatment.

Cases Presentation

The paper describes two patients undergoing long-term lithium therapy for psychiatric disorders.

Case 1

A 60-year-old female patient with a history of paranoid schizophrenia, type 2 diabetes mellitus, and hypothyroidism was admitted to the Department of Psychiatry due to deterioration of her mental condition. Upon admission, the patient was oriented autopsychically but disoriented allopsychically. She exhibited slurred speech, muscle tremors, and reluctance to take fluids.

Biochemical tests revealed:

- Lithium level: 2.8 mmol/L,
- Progressive hypernatremia (sodium 140–160 mmol/L),
- Rising creatinine levels (1.77 mg/dL),
- Increased levels of inflammatory markers.

The patient was transferred to the Department of Nephrology for normalisation of electrolyte imbalances, improvement of renal function and management of urosepsis. During hospitalisation, due to worse-

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ning consciousness, the patient was consulted by a neurologist, with no indication for lumbar puncture. The patient was fed via a nasogastric tube and hydrated with boiled tap water. After normalisation of sodium (142 mmol/L), creatinine (1.3 mg/dL) and CRP, the patient was transferred back to the Department of Psychiatry, where further neurological diagnostics (CT and MRI of the brain, lumbar puncture) revealed no pathology. Disorders of consciousness persisted during the hospital stay. Following recommendations from the consulting neurologist, and after excluding meningitis, the patient was transferred to the Department of Neurology. No antibodies indicating autoimmune encephalitis were detected. An EEG revealed abnormalities, and lithium-induced encephalopathy was diagnosed. Valproic acid therapy was initiated, leading to gradual improvement in the patient's condition. The patient was subsequently transferred back to the Department of Psychiatry to continue treatment.

Case 2

A 71-year-old female patient with bipolar affective disorder, treated with lithium, was admitted to the Department of Nephrology due to toxic serum lithium levels (2.8 mmol/L). Additionally, she presented with impaired verbal communication, elevated creatinine (2.28 mg/dL), elevated urea (88 mg/dL), reduced estimated glomerular filtration rate (eGFR 21 mL/min), and urine specific gravity of 1.005 g/mL. Acute kidney injury, stage 3, was diagnosed, and haemodialysis was performed. The patient's condition gradually deteriorated. The patient developed impaired consciousness and seizures. Administration of diazepam did not alleviate the symptoms. Computed tomography revealed no brain abnormalities. Persistent disorientation, tremors, tachycardia (HR 110/min), hypertension (190/100 mmHg) and fever (38.2°C) were observed, with creatinine 1.38 mg/dL and lithium 0.9 mmol/L. The patient was transferred to the Department of Anaesthesio-

logy and Intensive Care. Despite intensified treatment, the patient developed progressive hypotension, multiorgan failure and anuria. She experienced asystole. Laboratory tests showed progressive hypernatremia, reaching a maximum serum sodium level of 171 mmol/L.

In both patients, hypernatremia during lithium toxicity resulted from nephrogenic diabetes insipidus (NDI).

Discussion

Lithium carbonate is widely used in psychiatry for various indications. It increases serotonin release in specific brain regions, contributing to its antidepressant and anti-aggressive effects, and attenuates dopamine activity, which accounts for its anti-manic properties. Lithium also exerts neuroprotective and anti-inflammatory effects (which explains its therapeutic role in Alzheimer's disease and other neurodegenerative disorders). Additionally, it may mitigate the side effects of cranial radiotherapy for tumours and alleviate depression occurring after mild traumatic brain injury.

Adverse effects include inhibition of antidiuretic hormone, leading to increased urine output and the need for fluid replacement, not always accompanied by excessive thirst, and suppression of thyroid hormone release, which may result in hypothyroidism. Additionally, it inactivates calcium-sensing receptors (CaSR) in the parathyroid glands, leading to insufficient suppression of parathyroid hormone (PTH) secretion by calcium ions. The resulting increase in circulating PTH is a cause of hypercalcemia.

Lithium carbonate is rapidly and completely absorbed from the gastrointestinal tract, does not bind to plasma proteins, reaches stable serum concentrations after approximately one week, is not metabolised by the liver, and is excreted by the kidneys in its unchanged form. Drug clearance is directly dependent on renal clearance, and its half-life (T_{1/2}) is approximately 24 hours. Lithium is a medication with a narrow

therapeutic index. Sodium and water deficiency enhance proximal tubular reabsorption of lithium and prolong its excretion.

In long-term lithium therapy, maintaining serum concentrations in the range of 0.5–0.8 mmol/L is recommended to prevent relapses of affective disorders. Once the target concentration is achieved, monitoring can be performed less frequently: every month or every two months, and during remission every 2–3 months.

Lithium toxicity most commonly occurs due to dehydration (reduced renal lithium clearance) and drug interactions with metronidazole, NSAIDs, ACE inhibitors, angiotensin II receptor antagonists, and diuretics, particularly thiazide derivatives.

The first signs of toxicity appear at serum lithium concentrations >1.5 mmol/L, while life-threatening toxicity occurs at concentrations >2.0 mmol/L, which is an indication for urgent dialysis.

The most frequent renal manifestations of lithium toxicity include: acute kidney injury (AKI) – either prerenal or intrinsic (including acute tubular necrosis, ATN) – and nephrogenic diabetes insipidus (NDI).

Effects of lithium on the kidneys

Lithium-induced nephropathy was first described in 1977 by Hestbech et al.[5], who examined renal biopsy specimens from 14 patients treated with lithium for 2–15 years. In patients on long-term lithium therapy (over 10–20 years), clinical signs of nephropathy with characteristics of chronic tubulointerstitial nephropathy (CTIN) may develop. Histopathological examination revealed tubular atrophy and interstitial fibrosis in both the renal cortex and medulla, along with the characteristic presence of uniform and symmetrically distributed microcysts originating from distal tubules and collecting ducts. The presence of such cysts in the kidneys of normal size was confirmed by magnetic resonance imaging in 16 patients undergoing long-term lithium thera-

py. In a study of renal biopsy samples from 24 patients on long-term lithium therapy, Markowitz et al. [6] found a surprisingly high incidence of focal segmental glomerulosclerosis (FSGS), present in approximately half of the specimens. Other histopathological findings include minimal change disease (MCD), which appears to be more common than FSGS. Consequently, in most patients, no significant glomerular abnormalities are found, the prognosis is favourable, and complete remission typically occurs within several weeks after lithium discontinuation. In some patients with MCD confirmed on electron microscopy, reintroduction of lithium following recovery led to recurrence of proteinuria.

The most common complication of lithium therapy, however, is tubular dysfunction [2]. It is characterised by impaired urinary concentrating ability, which clinically manifests as varying degrees of polyuria and, not always, polydipsia. The main clinical signs of lithium-induced nephrogenic diabetes insipidus (Li-NDI) include polyuria, polydipsia, hypernatremia and low urine specific gravity. The urine concentrating capacity in 30–80% of patients undergoing long-term lithium therapy is reduced by approximately 15%, resulting in an increase in urine volume by 10–60% compared with the pre-treatment period.

Currently, the mechanism of polyuria in lithium-induced nephrogenic diabetes insipidus is believed to involve dysregulation of aquaporin-2 (AQP2) expression and insertion into the apical membrane of collecting duct principal cells. This leads to impaired expression of the epithelial sodium channel (ENaC) in the collecting duct. This channel is permeable to sodium and lithium. Permeability to lithium is 1.5–2 times greater than to sodium. Studies in healthy volunteers who received lithium carbonate for four weeks demonstrated a significant reduction in urinary AQP2 excretion and impaired urine concentrating ability, despite stimulation of the collecting duct with

desmopressin (dDAVP – a synthetic analogue of vasopressin). Lithium also decreases the density of vasopressin (AVP) receptors in the collecting duct, and the administration of vasopressin analogues such as dDAVP does not alleviate lithium-induced NDI. The treatment of choice is amiloride, which belongs to the group of diuretic drugs.

Conclusions

Management in both patients included discontinuation of lithium, a low-sodium diet, hydration with hypotonic fluids, and, in one case, haemodialysis. Lithium toxicity requires close clinical monitoring due to the risk of severe neurological complications. Regular assessment of serum electrolytes – particularly sodium, which plays a key role in lithium transport – is essential for proper patient management. Periodic evaluation of electrolyte levels (mainly Na^+) and renal function parameters is recommended, especially in conditions that may predispose to disturbances in water-electrolyte balance (such as infections, diarrhoea or old age). Adequate dietary sodium intake should be ensured in patients undergoing long-term lithium therapy, as lithium inhibits the tubular reabsorption of Na^+ .

The treatment of choice is amiloride, which belongs to the group of diuretic drugs. It blocks epithelial sodium channels (ENaC) in collecting duct principal cells, which become impermeable to sodium and lithium. It is the best-studied and most promising agent for the management of Li-NDI. By blocking ENaC, amiloride inhibits lithium uptake into the collecting duct principal cells, leading to an 87% reduction in intracellular lithium concentration, and its administration can reduce urine output by approximately 50%. A study involving patients with bipolar disorder treated with lithium demonstrated that administration of amiloride 10 mg daily for 6 weeks significantly increased the maximum urine osmolality in the dDAVP-stimulated urine concentration test [7]. Amiloride is also believed to have cytoprotective effects

on collecting duct cells, preventing structural damage associated with long-term lithium exposure.

The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) concluded that lithium is dialyzable, supported the use of extracorporeal treatment in severe lithium poisoning and made the following recommendations [8]: extracorporeal treatment (hemodialysis is preferred) is recommended in severe lithium poisoning if kidney function is impaired and the serum lithium concentration is >4.0 mEq/L, or in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of the lithium concentration. Extracorporeal treatment is suggested if lithium is >5.0 mEq/L, significant confusion is present, or the expected time to reduce lithium to <1.0 mEq/L is >36 hours. This treatment should be continued until clinical improvement is apparent or lithium is <1.0 mEq/L. Extracorporeal treatment should be continued for a minimum of 6 hours if lithium is not readily measurable. Continuous renal replacement therapy (CRRT) is an acceptable alternative treatment.

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