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Case Report

Multiple Endocrine-Related Complications of Lithium Therapy in a Patient with Low-Grade Meningioma

Sajjad Hussain (MBBS, MRCP, FCPS), Abdullah Shamshad (MBBS, MRCP, FCPS)
Talha Rauf (MBBS, RMP), Muhammad Zeeshan Zafar (Pharm-D, MPhil, RPh)

[1]*Medical Specialist, Siddique Family Hospital, Gujranwala;* [2]*Medical Specialist, Chaudhary Hospital Gujranwala;* [3]*Medical Officer, Gujranwala medical college, Gujranwala;* [4]*Research Associate, College of Pharmacy, University of Sargodha*

ABSTRACT

Lithium is a first-line treatment for bipolar disease. It is not only associated with thyroid dysfunction but also with Primary Hyper Para Thyroidism (PHPT), nephrogenic diabetes insipidus, and an increased risk of end-stage renal disease. An elderly female patient on long-term lithium for 'bipolar disorder' presented in an acute confusional state with hypercalcemia and renal impairment. Further investigations confirmed PHPT, euthyroid goitre, and medullary nephrocalcinosis. Following a Para thyroidectomy, she developed an acute neurological deficit. A Computed Tomography (CT) scan of the head demonstrated a large meningioma. Following resection of the meningioma, she developed diabetes insipidus and orofacial dyskinesia, probably related to lithium therapy. Prolonged respiratory support in intensive care settings necessitated a tracheostomy by an open approach, due to the goitre, which was also associated with lithium therapy. This case illustrates the spectrum of endocrine related complications from lithium use and the need for biochemical monitoring in patients on long-term treatment.

Keywords: Lithium; Endocrine; Complications; Meningiomas

INTRODUCTION

Lithium has been established as a mood stabilizer since its discovery by Dr John Cade in 1948 and is an effective treatment for bipolar disorder [1,2]. It however interacts with the function of several other organ systems and endocrine pathways [3]. Although thyroid dysfunction is the most common endocrine side effect of lithium, chronic lithium use can rarely lead to hypercalcemia and renal dysfunction [4,5]. Lithium causes a range of thyroid abnormalities such as goitre formation, hypothyroidism and hyperthyroidism by affecting thyroid hormone production and release and by direct action on the thyroid gland [6]. While goitre is common among patients on long-term lithium, some goiters are associated with significant symptoms and may necessitate resection [7]. Lithium also causes a progressive decline in renal function in up to 20% of patients [8], and exerts toxic effects mainly at the distal renal tubule [9]. Monitoring patients on lithium is important. The National Institute of Clinical Excellence (NICE) recommend six-monthly tests of thyroid and renal function and more frequent monitoring if the deterioration is noted [10]. It is also suggested that calcium levels be monitored in these patients on an annual basis [11]. The patient described in this case report developed multiple endocrine related complications of lithium therapy including PHPT requiring parathyroidectomy, renal dysfunction and multinodular goitre which complicated the recovery of the patient following craniotomy for a low-grade meningioma. This case illustrates the importance of regular biochemical monitoring of patients on lithium therapy and the need to rule out organic brain pathology in adult patients presenting with psychiatric symptoms.

CASE PRESENTATION

A female patient in her 60s who was on long-term lithium therapy for over 20 years for 'manic depression and bipolar

Corresponding author: Muhammad Zeeshan Zafar, Department of Pharmacy, University of Sargodha, Gujranwala, Pakistan, E-mail: shumughal11@gmail.com

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disorder' was admitted to the hospital with an acute confusional state. She had a background of stage 3 Chronic Kidney Disease (CKD) and euthyroid goitre. Her regular medications included lithium and risperidone. She was confused, disorientated, and dehydrated on admission. On examination, no other abnormality was found (Figures 1 and 2).

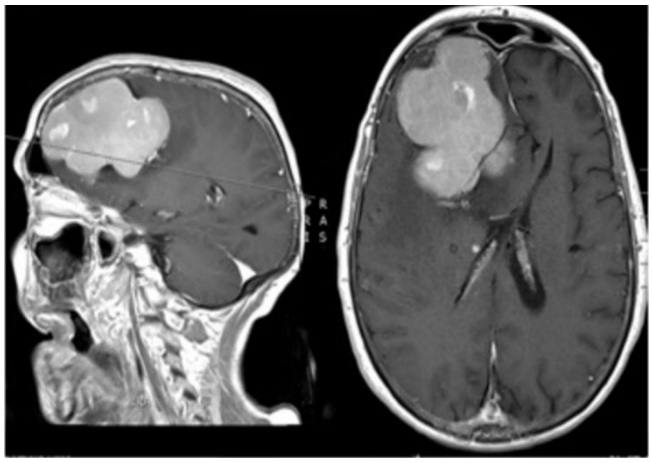

Figure 1: MRI head (T1WI with contrast) showed the 8 cm maximum diameter mass in right frontal lobe.

Investigations if relevant

Initial blood tests demonstrated hypercalcaemia (adjusted calcium 2.83; normal range 2.2 mmol/L-2.60 mmol/L), and reduced eGFR of 43 ml/min/1.73 m^2. Her lithium level was 1 mmol/L, which was above the therapeutic range (0.4-8 mmol/L) but below toxic levels (72 nmol/L). The 24-hour urinary calcium excretion was 5.6 mmol/24 h (normal range 2.5-7.5 mmol/24 h), which is consistent with a diagnosis of PHPT. Preoperative localisation scans for PTHT included an ultrasound scan of the neck which demonstrated a benign-appearing multinodular goitre with evidence of an enlarged parathyroid and a sestamibi parathyroid scan that showed abnormal uptake in the left inferior location.

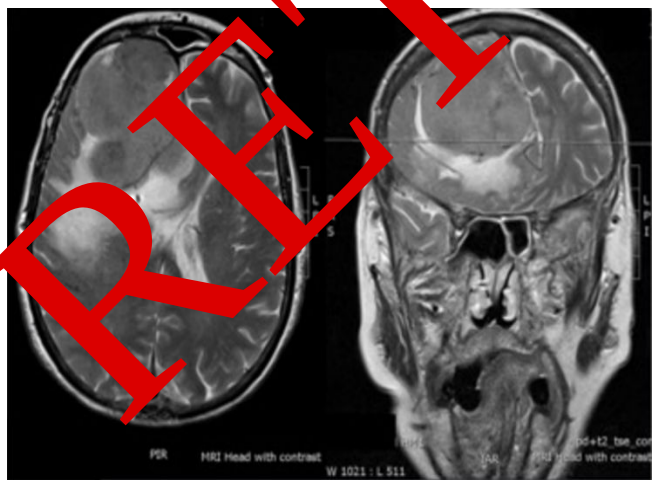

Figure 2: MRI head (T2WI) showed meningioma with associated vasogenic oedema.

Differential diagnosis if relevant

Not relevant

Treatment if relevant

The patient's initial confusional state resolved with hydration and she was commenced on warfarin for treatment of pulmonary embolism. Approximately eight months after acute admission, she underwent an elective neck exploration. Intra-operatively, three enlarged parathyroid glands (left inferior, right superior and right inferior) were excised. The fourth gland (left superior) was identified in the orthotopic location, thought to be of normal size and therefore preserved. Histology showed parathyroid hyperplasia. On the first day post-operatively, she developed a sudden onset of left hemiparesis with reduced Glasgow Coma Scale (12/15: E4, V3, M5), suggesting potential brain decompensation due to significant mass effect. Her husband later reported that he noticed that the patient had been neglecting her left side of the body during daily activities such as dressing for several weeks before her operation. A CT head showed a 6 cm maximum diameter mass in the right frontal lobe with areas of calcification and surrounding oedema causing a marked mass effect. There was hyperostosis in the right frontal bone adjacent to this mass. MRI of the head confirmed the diagnosis of a meningioma with associated vasogenic oedema, but there was no evidence of sinus invasion. She then underwent an urgent craniotomy two days after the parathyroid surgery. The frontal lobe tumour was completely excised and she was subsequently treated in the neurosurgical intensive care unit. Two days after craniotomy, she developed significant diuresis of up to 500 ml/hr and rapidly developed a negative fluid balance. Further investigation revealed hypernatremia (serum sodium of up to Na 165; normal range 134-143 mmol/L), high serum osmolality of 327 mOsm/kg (normal range 275-295 mOsm/kg), low urine osmolality of 227 mOsm/kg, mildly raised serum adjusted calcium of 2.63 (normal range 2.2-2.60 mmol/L) and a normal serum PTH of 37 ng/L (normal range 15-67 ng/L)- features suggestive of diabetes insipidus and persistent mild PHPT. She was commenced on intravenous fluids, high dose DDAVP® (Desmopressin) and co-amilofruse for five days. As she required prolonged respiratory support in the intensive care unit, a percutaneous tracheostomy was attempted. Unfortunately, this failed due to the presence of a dominant isthmus nodule of the multi-nodular goitre. A further neck exploration was performed (on day eight after the initial parathyroidectomy) and she underwent partial excision of the left superior parathyroid gland (to treat mild persistent hypercalcaemia), isthmectomy (to gain access to her airway) and tracheostomy. Histologically, the thyroid isthmus and parathyroid tissue showed hyperplastic change. The histology of the intracranial lesion showed a grade 1 benign meningioma.

Outcome and follow-up

Following her return to the intensive care unit, her calcium, other electrolytes and renal function returned to normal, and she was slowly weaned off the ventilator. Her tracheostomy was successfully removed after two months and she was discharged

from the hospital about 3 months after the elective admission for parathyroidectomy. A multidisciplinary approach was adopted in follow-up, and she was monitored in the community by the brain injury team, psychiatry, neurology, and endocrinology.

RESULTS AND DISCUSSION

Lithium-induced primary hyperparathyroidism

Lithium-induced hyperparathyroidism is well documented in the literature after the first report in 1973. Since then, multiple cases have shown parathyroid hyperplasia to be linked to lithium treatment, but independent of duration or dose of lithium. Only a small proportion of patients on lithium become hypercalcaemic [12,13]. Reported mechanisms include the inhibition of inositol monophosphatase, inhibition of glycogen synthase-3 and interaction with calcium sensing receptors in the chief cells of parathyroid glands. The mainstay of lithium-associated PHPT is surgical treatment. Surgery has been shown to improve psychosomatic symptoms in 90%-97% of patients. Recently, calcimimetic therapy such as cinacalcet has been used in the treatment of lithium-induced hyperparathyroidism with or without discontinuation of lithium.

Lithium and the thyroid gland

Lithium concentrates itself in the thyroid gland and can cause multiple thyroid abnormalities such as hypothyroidism and hyperthyroidism by inhibiting thyroid hormone synthesis or by predisposing to autoimmune thyroiditis. Goitre formation is thought to be due to the activation of pro-proliferative glycogen kinase and Wnt/beta signaling pathways [14]. Euthyroid goitre is the most common clinical finding and has been demonstrated in multiple studies. While benign multinodular goitre is often asymptomatic, it may cause compressive symptoms in several patients necessitating surgery. In addition, it can complicate bedside percutaneous tracheostomy. Compared with standard open tracheostomy, percutaneous tracheostomy has the benefits of a smaller incision, shorter operative time, lesser intraoperative bleeding and reduced risk of infection. However, the risk of injury to the thyroid is greater with percutaneous tracheostomy, especially in patients with short necks and large thyroid glands [15]. While injury to the thyroidea ima artery during percutaneous tracheostomy is potentially life-threatening, there are cases reported in the literature that highlight how puncturing the thyroid isthmus during a percutaneous tracheostomy puncture is safe [16,17].

Renal effects of lithium

Nephrotoxicity can be seen within a few weeks of lithium commencement. It can cause a decline in renal function and in rare cases, end stage renal failure [18]. Medullary nephrocalcinosis is a well-known complication of PHPT secondary to lithium use. Lithium is thought to cause dysregulation of aquaporins on Epithelial sodium Channels (EnAC) on renal tubular cells leading to impairment of the concentrating ability of the kidneys, predisposing patients to diabetes insipidus. Monitoring of renal function is therefore important and the NICE guidance advocates testing prior to commencement of lithium and every six months, with more frequent tests if there was evidence of impaired renal function.

Meningioma presenting as bipolar disorder

Meningiomas account for 24% of all primary brain and central nervous system tumours and are homogenous, circumscribed, enhancing extra-axial lesions that can lead to mass effect on the underlying brain. Despite being the most common benign brain tumours, meningiomas can remain undetected for long periods as they can be asymptomatic or present with insidious psychiatric symptoms such as depression and apathy. Multiple case studies have shown this to be a difficulty for psychiatrists where meningiomas have been the underlying cause of psychiatric symptoms. There is currently a debate about when a clinician should consider neuroimaging for patients with a known psychiatric illness. A set of indications for neuroimaging has been proposed; this includes neurological signs or symptoms, pre-existing brain pathology, significant change in presentation, family history of neurological disorders, history of head injury, seizures, acute onset or delirium-like picture, or prior electroconvulsive therapy. In this case, the patient has unfortunately developed multiple long-term endocrine complications of lithium use; which in hindsight was not warranted. While lithium remains an indispensable mood stabilizer in bipolar disorder, its chronic use necessitates the monitoring of the function of the thyroid gland, parathyroid glands and kidneys through periodic blood tests. Avoiding episodes of lithium toxicity, keeping mean lithium levels within the low therapeutic range when possible and considering once-daily dosing are the overall strategies for improving the management of the patients on chronic lithium treatment. In the literature, there is limited evidence of chronic lithium treatment resulting in the development of several endocrine complications in the same patient. This report should increase awareness of these complications and the timely involvement of multidisciplinary teams in managing these patients.

CONCLUSION

Chronic lithium use may lead to hypercalcemia and PHPT, which may manifest as an acute confusional state. Imaging of the brain should be considered in patients with new onset psychiatric symptoms or other specific indicators of organic brain pathology. This report highlights the need for increased awareness of the endocrine complications of chronic lithium therapy in psychiatric disorders and the institution of appropriate monitoring measures.

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