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CASE REPORT

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A Case of Pseudotumor Cerebri Associated with Lithium Use

Özge TÜRKOĞLU[1], Hafize Nalan GÜNEŞ[2], Ayşe Elif ANIL YAĞCIOĞLU[2]

ABSTRACT

Pseudotumor cerebri (PC), also known as idiopathic intracranial hypertension, is characterized by increased intracranial pressure in the presence of normal brain imaging and cerebrospinal fluid analysis. Papilledema, headache and visual loss are frequently observed clinical signs and symptoms. Although the pathogenesis of pseudotumor cerebri is not known exactly, different risk factors have been identified. Drugs such as growth hormone, tetracycline and retinoic acid have been reported to be associated with PC. Additionally, in the literature, there are case reports indicating the development of PC associated with lithium use. The aim of this case report is to discuss a 26-year-old patient who was started on lithium with a diagnosis of bipolar disorder and presented to the emergency service with complaints of headache and visual loss 4 months after the initiation of treatment and was diagnosed with PC associated with lithium use. It is important to be aware of the risk of PC development in patients treated with lithium and to rapidly evaluate patients in this respect in case of clinical symptoms such as headache and vision problems because of the risk of permanent vision loss.

Keywords: Intracranial Hypertension, Lithium, Papilledema, Pseudotumor Cerebri

INTRODUCTION

Pseudotumor cerebri (PC), also called idiopathic intracranial hypertension, is a clinical condition characterized by symptoms and signs such as papilledema, visual loss, headache caused by increased intracranial pressure, in which cerebrospinal fluid (CSF) examination and brain imaging are usually normal and there is no other etiology responsible for intracranial pressure increase. Patients may experience intractable headaches significantly impairing daily life and there is a risk of permanent vision loss. It is reported that PC is more common in overweight women aged 15-44 years (Kesler and Gadoth 2001).

Although the pathophysiology of PC is not known clearly, different risk factors have been defined. Some systemic diseases, vitamin deficiencies and excesses, anemia, hereditary conditions, medications such as growth hormone, tetracycline, retinoic acid have been reported to be associated with PC (Levine and Puchalski 1990, Blethen 1995, Friedman 2005, Kelly et al. 2009, Mollan et al. 2009). There are also case reports of PC associated with lithium use (Saul et al. 1985, Levine and Puchalski 1990, Ames et al. 1994, Callens et al. 2012, Gölbaşı and Gülpek 2012), which is a mood stabilizer mainly used in the treatment of bipolar affective disorder (Malhi et al. 2017).

Although certain neurological side effects of lithium such as memory impairment and postural tremor are well known, there are rare side effects (Kesebir et al. 2001, Alp et al. 2023). There are case reports on lithium associated PC, which is observed more rarely, and it is important to increase the awareness in terms of its outcomes. In this case report, it is aimed to discuss a patient who developed PC after lithium initiation and whose symptoms recovered almost completely after discontinuation of the drug, to review the available literature and to increase awareness on the matter by drawing attention to PC as a rare side effect. The patient was informed about the case report and her consent was obtained.

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[1]Psychiatrist, Soma State Hospital, Department of Psychiatry, Manisa, Turkey; [2]Assoc. Prof., Ankara Education and Research Hospital, Neurology Clinic, Ankara; [3]Prof., Hacettepe University, Faculty of Medicine, Department of Psychiatry, Ankara, Turkey.

e-mail: ozge.turkoglu@windowslive.com

CASE

A 26-year-old woman presented to the outpatient clinic with complaints of sadness, loss of interest and pleasure, difficulty in concentrating. It was learned that her complaints had started at the age of 12 with sadness, loss of interest, worrying that something might happen to her relatives, restlessness, shortness of breath, and palpitation. It was also learned that there had been marital conflict in her family during her childhood and adolescence, and at the age of 15 she had a period of hypomania with decreased sleep duration, increased energy, increased amount of speech and thought acceleration which had been followed by a period of depression with sadness, loss of interest and pleasure, increased sleep and appetite, and suicidal thoughts. She was started on fluoxetine 20 mg with the diagnosis of "Depressive Episode", and since she did not improve after using it regularly for a month, trazodone 50 mg was added to her regimen, however there had been no change in her complaints. In addition, it was learned that the patient had 4 similar episodes of hypomania followed by depression in her high school years and she was put on vortioxetine 10 mg, however, she did not improve after using it regularly for a month, and the episodes recurred spontaneously. In the 2nd year of college, she had a depressive episode with sadness, loss of interest and pleasure, concentration problems, increased sleep and appetite due to increased responsibilities related to her studies. Although, she did not consult a physician, her complaints improved spontaneously. While studying in the 3rd year of college, she had a hypomania episode with increased self-confidence and energy, decreased sleep duration and accelerated thoughts. After her cousin had a traffic accident during the summer holiday, she had a depressive episode lasting 4-5 months and was put on escitalopram 10 mg/day for 1 month but did not improve. She received Cognitive Behavioral Therapy for 5 months and showed improvement, not having any complaints for approximately 1.5 years. After starting her master's degree, her depressive symptoms started again due to difficulties in academic studies and problems in interpersonal relationships. After this period, a hypomanic episode with increased self-confidence, accelerated thoughts, overspending and increased speech amount, and then a depressive episode with feeling inadequate, pessimism about the future, sadness, loss of interest and pleasure started. She applied to the outpatient clinic with these depressive complaints that had been continuing for 5-6 months (Figure 1). It was observed during mental status examination that her appearance was obese (body mass index 36.1 kg/m^2), her speech rate and amount were normal, she had depressed mood and appropriate affect. Her thought content included depressive themes such as feeling inadequate and unsuccessful about the master's degree and pessimism. She had regular associations and normal psychomotor activity. The patient was diagnosed with "Bipolar Disorder-type 2, Depressive Episode". The Hamilton Depression Rating Scale score was 14. Lithium 600 mg/day was started. After 1 week, lithium was increased to 900 mg/day when the serum concentration was determined to be 0.53 mEq/L. Two months later, sertraline 50 mg/day was added to the treatment considering that the patient's depressive symptoms partially decreased but there was no adequate response. The serum concentration of lithium was 0.77 mEq/L. It was learned that she had tremor in her hands and tinnitus after lithium was initiated and these side effects did not significantly affect her daily life. Laboratory analysis revealed no pathology in thyroid and renal function tests and complete blood count. The patient who responded to the treatment was admitted to the emergency service with complaints of headache and visual loss 4 months after lithium was started. During physical examination, papilledema was observed in both eyes. No other pathological findings were detected during physical and neurological examination, and she was euthymic during mental status examination. The patient who was admitted to the neurology service was found to have normal brain diffusion magnetic resonance imaging (MRI), brain MR venography and cervical MRI. In the orbital MRI, both optic nerves were slightly tortuous and CSF distance had increased (Figure 2). There was no pathological contrast enhancement. In the CSF analysis, glucose was 54 mg/dL (N>60% of plasma glucose), protein was 219.6 mg/dL (N=20-45 mg/dL), chloride was 121.7 mEq/L (N=110-125 mEq/L), CSF opening pressure was 180 mm/H2O and closing pressure was 150 mm/H2O. It was reported that there was no growth in CSF culture, no microorganisms and leukocytes were observed, TORCH panel IgMs, ANA, anticardiolipin and ANCA in vasculitis panel were negative, and the patient who had no other known medical disease in her history was diagnosed with PC. Since no other suspected causative factor other than lithium use was found, lithium was discontinued. The treatment was changed to sertraline 50 mg/day and aripiprazole 10 mg/day. The patient's PC-related symptoms and signs improved almost completely within 1 month. In the follow-up examination, sertraline was discontinued and aripiprazole 10 mg/day was continued due to accelerated thoughts, increase in the amount of energy and spending money. After 3 months, it was learned that she was in remission in terms of PC. Evaluation of the patient with the Naranjo Adverse Drug Reactions Probability Scale showed a total score of 7 and the causality between lithium and PC was determined to be probable.

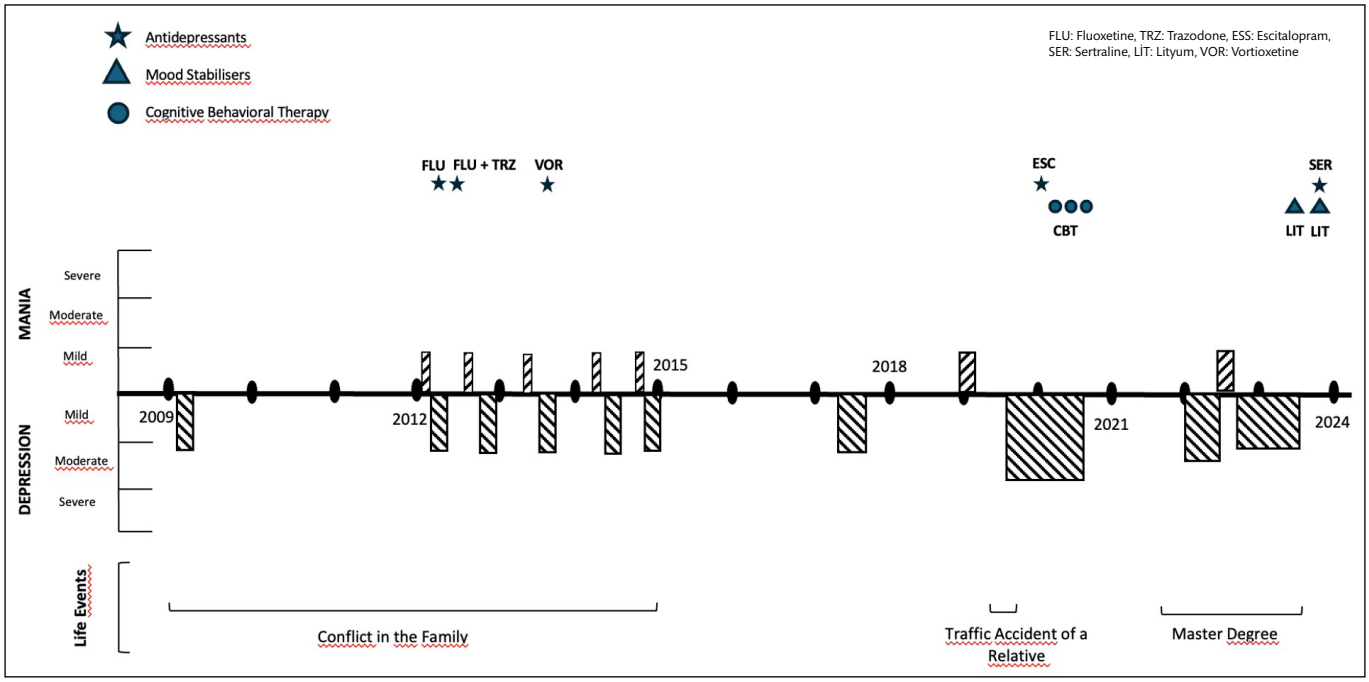

Figure 1. Life Chart

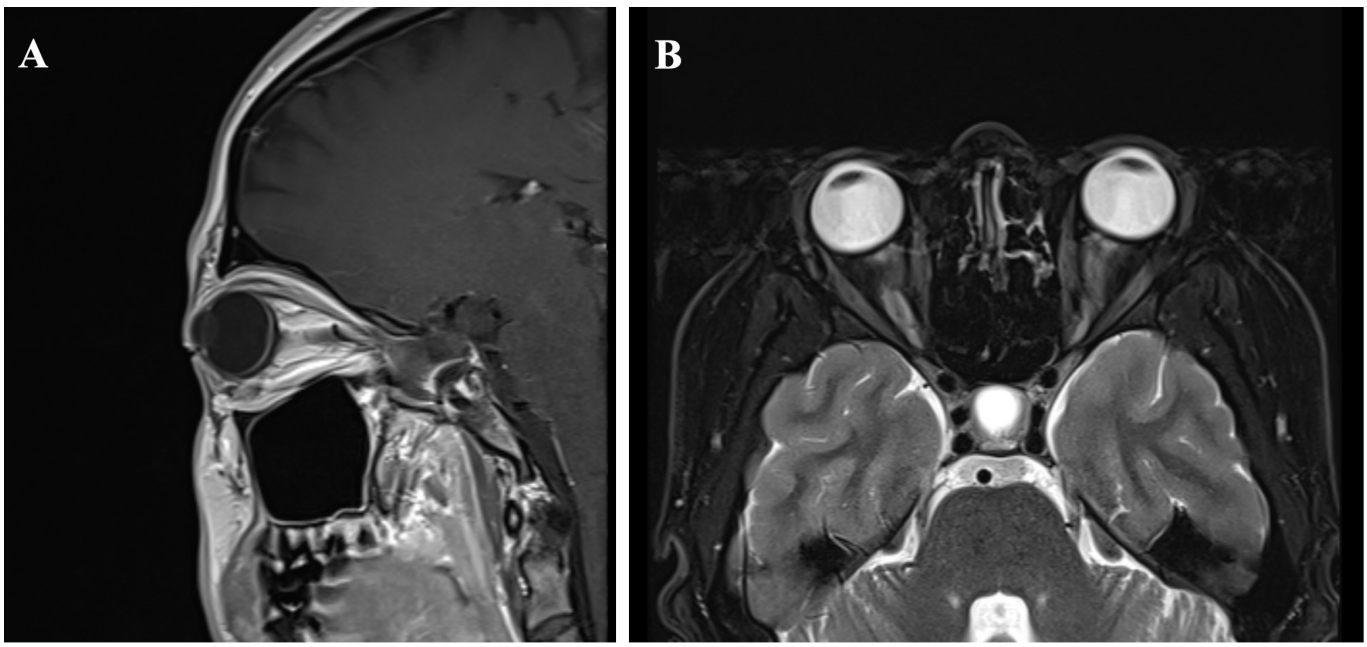

Figure 2. Sagittal T1 (A) and axial T2-weighted (B) orbital magnetic resonance imaging

DISCUSSION

In this report, a case who developed headache and visual loss 4 months after the initiation of lithium treatment and was diagnosed with PC was presented. PC is a clinical condition characterized by specific signs and symptoms caused by increased intracranial pressure in the absence of any other cause explaining the increased intracranial pressure. Headache and papilledema are the most common and 'classic' presentations of PC (Chen and Britton 2023). Papilledema, normal neurologic examination, exclusion of secondary causes of increased intracranial pressure by brain imaging, normal CSF components and elevated CSF opening pressure (≥ 250 mm/H2O) are the main diagnostic criteria for PC (Friedman et al. 2013). The diagnosis is considered definitive if the first four of these criteria are met, and probable if the CSF opening pressure is lower than that specified for definitive diagnosis (Friedman et al. 2013). It has been reported that a subgroup of patients with incidentally detected papilledema may have less headache and lower CSF opening pressures compared

to typical PC patients (Chen and Britton 2023). Other symptoms associated with PC include dizziness, pulsatile tinnitus and cognitive impairment. Characteristic radiological findings supporting the diagnosis include increased CSF distance around the optic nerve, protrusion of the optic nerve head, tortuous course of the optic nerve, empty sella turcica, and stenosis of the transverse venous sinuses (Bidot et al. 2015, Moreno and Del Carpio-O'Donovan 2023). In this case report, the patient who presented with visual loss and headache complaints was diagnosed with PC based on the finding of papilledema on examination, absence of any other pathology on neurological examination, exclusion of possible secondary causes by CSF analysis, brain imaging and other examinations, despite the fact that the CSF opening pressure was not as high as expected. It was thought that the increase in protein in CSF analysis might be related to the traumatic LP. In addition, the finding that "both optic nerves were slightly tortuous and CSF distance increased" on orbital MRI was evaluated as findings supporting increased intracranial pressure.

Lithium causes many acute and long-term side effects that are not only related to toxicity (Grandiean and Aubry 2009). Lithium, the side effects on renal, thyroid and gastrointestinal system functions of which are well known, also has neurological side effects such as postural tremor, memory impairment and slowed reaction time. In addition, there are case reports of PC due to lithium use (Callens et al. 2012). In a review, it was reported that 16 lithium users were diagnosed with PC and the causal link between lithium use and the development of PC was strong in 2 of the cases (Callens et al. 2012). In the case reports, it was observed that the time between the initiation of lithium and the development of PC varied from 6 months to 2 years (Kelly et al. 2009, Ames et al. 1994), and in a 13-year-old patient who used lithium for bipolar disorder, symptoms started 3 weeks after the dose increase (Hexom and Barthel 2004). In the presented case, PC developed 4 months after the initiation of lithium. In most of the reported cases in the literature, lithium serum concentrations were within the therapeutic range (0.5-1.0 mEq/L) (Hexom and Barthel 2004). In the presented case, the most recent lithium serum concentration was 0.77 mEq/L. Additional risk factors such as being overweight, female gender and minocycline use have also been reported in some cases in the literature (Hexom and Barthel 2004, Jonnalagadda et al. 2005). In this case, there was no history of any other drug use or medical illness other than lithium that might be associated with increased intracranial pressure. Obesity and female gender were other possible risk factors.

Although there are reports in the literature showing that symptoms and signs improved after lithium discontinuation in patients who developed lithium-associated PC (D'Anglejan Chatillon et al. 1989), cases requiring acetazolamide treatment (Kelly et al. 2009) and shunt operation (Levine and Puchalski 1990) have also been reported. If a patient on lithium treatment is diagnosed with PC and there is no other more probable cause, it is recommended to discontinue lithium treatment (Callens et al. 2012). However, it is suggested that lithium treatment may be restarted in certain circumstances, such as when the patient has clearly benefitted from lithium in previous maintenance treatment, when there is an unclear relation between lithium and the onset and course of PC, or when the patient's condition has clearly worsened after discontinuation of lithium treatment (Callens et al. 2012). In the presented case, a significant improvement in symptoms was observed within 1 month after lithium discontinuation and no further treatment was required in the patient who was followed up in remission.

Lithium has pharmacological activity through multiple signal transduction pathways and cellular processes (Alda 2015). Glycogen synthase kinase 3 (GSK3), cAMP response element binding protein (CREB) and Na^+/K^+ ATPase-related mechanisms are thought to be among the mechanisms of action of lithium (Alda 2015). The exact mechanism of how lithium causes PC is not clear. It has been suggested that increased intracellular Na^+ concentrations due to Na^+/K^+ pump inhibition in neurons may lead to PC secondary to increased intracellular edema (Saul et al. 1985). Other proposed mechanisms include Na^+ retention with increased antidiuretic hormone (ADH) in the CSF, edema due to increased glucose uptake into the central nervous system, and lithium causing PC indirectly by causing hypothyroidism or weight gain (Hexom and Barthel 2004).

In conclusion, the fact that PC developed 4 months after the initiation of lithium, there was no history of other drug use or medical illness that could explain it, and the patient was followed up in remission with improvement of symptoms after lithium was discontinued suggested a strong causality between the development of PC and lithium. It is important to be aware of the risk of developing PC in patients on lithium treatment, and to examine symptoms such as headache and visual problems, especially in the presence of additional risk factors. The risk of permanent visual loss caused by pseudotumor cerebri makes it the responsibility of psychiatrists to rapidly evaluate patients in the case of the development of PC in patients on lithium treatment.

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