Turkish Journal of Psychiatry 2024;35(2):150–155
https://doi.org/10.5080/u27074

Catatonia Due to Lithium Neurotoxicity: A Case Report

Anıl ALP[1], Tahsin ROLLAS[2], Elçin ÖZÇELİK EROĞLU[3], M. İrem YILDIZ[4], A. Elif ANIL YAĞCIOĞLU[5], Berna Diclenur ULUĞ[6]

ABSTRACT

Lithium may cause toxicity as it has a narrow therapeutic range. Lithium intoxication may manifest in the form of acute, acute on chronic and chronic intoxication. Neurotoxicity is a common component of chronic lithium intoxication and the symptoms include tremor, ataxia, dysarthria, extrapyramidal symptoms, hyperreflexia, seizures and status epilepticus. Although rare, catatonia could as a manifestation of lithium neurotoxicity. In this report, we present a patient with bipolar disorder presenting with catatonic symptoms secondary to lithium intoxication. We will discuss the risk factors, differential diagnosis and the treatment of catatonic symptoms. Lithium neurotoxicity may present with various clinical symptoms including catatonia, and differential diagnosis should be made well in such cases. If lithium neurotoxicity is suspected, rapid and appropriate intervention is required to prevent permanent neurological damage.

Keywords: Lithium, Neurotoxicity, Catatonia

INTRODUCTION

Lithium is an effective drug widely used in the maintenance treatment of recurrent depression and bipolar disorder (Malhi et al. 2017). Due to its narrow therapeutic range, it should be used carefully to prevent lithium intoxication (Decker et al. 2015). Lithium intoxication is classified as acute, chronic intoxication and acute on chronic intoxication (Baird-Gunning et al. 2017). In addition to frequent gastrointestinal symptoms, neurological, nephrological, cardiovascular and endocrine symptoms can be seen in acute lithium intoxication; nephrotoxicity and neurotoxicity are more common in chronic lithium intoxication. The most common clinical findings of chronic lithium intoxication are ataxia, coarse tremor, dysarthria, dyskinesia, extrapyramidal symptoms and hyperreflexia (El Balkhi and Mégarbane 2017). Although many neurological symptoms associated with lithium neurotoxicity have been described, there are few reports of catatonia (Desarkar et al. 2007, Medda et al. 2018).

The differential diagnosis, risk factors and treatment of catatonia occurring during lithium intoxication will be discussed in this case report.

CASE

A 60-year-old female patient presented with depressed mood, insomnia, loss of appetite, suicidal thoughts and delusions of persecution. Her first complaints started in 1990 as talking and spending more than usual, hyperactivity, and a distinct decrease in sleep duration and need. She was hospitalized with a diagnosis of bipolar disorder manic episode, and lithium treatment was started. The patient, who continued lithium treatment regularly until 2019, started using lithium irregularly in early 2019 due to a diagnosis of hypertension and edema in her legs. Shortly after she started using lithium irregularly, depression, social withdrawal, insomnia, restlessness, suspiciousness, auditory hallucinations, and persecutory delusions began; she was hospitalized in a psychiatry ward with a diagnosis of bipolar disorder depressive episode accompanied by psychotic symptoms and was discharged after her symptoms improved with lithium 1200 mg/d and quetiapine 100 mg/d. Due to the high plasma creatinine level and low glomerular filtration rate (GFR) in the control visits, the lithium dose was reduced to 600 mg/d. The patient did not attend to the follow-up

Received: 10.01.2022, **Accepted:** 05.05.2022, **Available Online Date:**18.11.2023

[1, 2]Resident in Psychiatry, [3, 4]Assoc. Prof, [5, 6]Prof., Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey.

e-mail: anil_alp@hacettepe.edu.tr

visits regularly and she was observed to display depressive and psychotic symptoms at the outpatient clinic in 2020. In laboratory tests, plasma creatinine level was 1.47 mg/dL (reference range: 0.51-0.95) and GFR value was measured as 38 ml/min/1.73m^2. The treatment was adjusted as lithium 300 mg on alternate days, quetiapine 100 mg/d, alprazolam 1 mg/d, mirtazapine 15 mg/d, and trifluoperazine 1 mg/d. The patient was hospitalized in our inpatient clinic due to lack of improvement in her depressive symptoms and suicidal thoughts.

In her physical examination at her admission to the inpatient clinic, bilateral pretibial +1 pitting edema was observed. In her neurological examination, bilateral cogwheel rigidity, which was more prominent on the left, was present. Her mood was depressed, her affect was blunted and she had delusions of persecution and reference, together with suicidal ideation in the mental state examination. In addition, she had auditory hallucinations and lacked insight regarding her psychiatric illness. No signs of catatonia were detected. She was diagnosed with Bipolar Disorder Depressive Episode with Psychotic Features. The Hamilton Depression Rating Scale (HAM-D) score was calculated as 35 (Akdemir et al. 1996). Complete blood count (CBC) and liver function tests (LFT) results were normal, and blood electrolyte levels were in normal range. In kidney function tests (KFT), creatinine was 1.49 mg/dL and GFR was 37.5 ml/min/1.73m^2. Serum lithium level was 0.56 mmol/L. Routine urinalysis and posteroanterior chest X-ray were normal.

Olanzapine 5 mg/d and sertraline 25 mg/d treatments were started for the treatment of depressive and psychotic symptoms. Lithium was discontinued due to irregularities in the KFT. After increasing the dose of olanzapine treatment to 10 mg/d, neurologic examination revealed bradykinesia, Myerson's sign, tremor and ataxic gait, and an increase in cogwheel rigidity. The severity of parkinsonism symptoms increased in the follow-up, and disorientation appeared. The patient's temperature was 37.8°C, other vital signs were normal. Serum lithium level was measured as 0.37 mmol/L, creatinine as 1.34 mg/dL, GFR as 46 ml/min/1.73m^2. In addition to CBC, LFT, and blood electrolyte levels, creatinine kinase (CK) and myoglobin levels, which can be supportive laboratory findings for the differential diagnosis of neuroleptic malignant syndrome (NMS), were studied. These were within the normal range. In the physical examination, no findings regarding an infection could be detected. C-reactive protein (CRP), sedimentation, procalcitonin, Covid-19 PCR (Polymerase Chain Reaction) test, complete urinalysis, urine culture and posteroanterior chest X-ray tests were requested for the patient for whom the department of infectious diseases was consulted. CRP value was 0.454 mg/dL (reference range: 0-0.8), sedimentation value was 8 mm/hour (reference range: 0-25). With these findings, the department of the infectious diseases concluded that there was no sign of an infectious clinical process. Brain magnetic resonance imaging (MRI) was performed but did not reveal any pathological findings other than mild cerebral atrophy. Her electroencephalography (EEG) was normal. In the follow-up of the patient, it was observed that ataxic gait intensified, truncal ataxia appeared, her speech was dysarthric, and intentional tremor accompanied postural tremor. With the newly emerging cerebellar findings, lithium neurotoxicity was considered in the differential diagnosis. All psychotropic drugs including olanzapine were discontinued on the confirmation of lithium intoxication diagnosis by the neurology department.

Four haemodialysis sessions, one lasting four hours and the other three lasting six hours, were conducted to accelerate lithium excretion, until the serum lithium level was zero. After haemodialysis, tremor, bradykinesia, postural instability, dysarthria and disorientation improved, Myerson's sign disappeared. The severity of ataxia, tremor and cogwheel rigidity continued to decrease.

Neurocognitive tests were performed as soon as the clinical condition of the patient allowed testing, following the improvement of acutely developed neurological findings after haemodialysis treatment. In the neuropsychological examination of the patient; mini mental test and modified mini mental test were performed to evaluate general cognitive performance; trail making A & B test and digit span test to evaluate attention and executive functions; verbal and semantic fluency tests to evaluate the flow and speed of verbal production and working memory; clock drawing test to evaluate visual-motor functions and planning and abstract thinking skills. It was determined that the patient had mild impairment in general cognitive performance and executive functions.

Lorazepam 2 mg/d treatment was started as concomitant symptoms of catatonia were observed including mutism, echopraxia, mannerism, negativism and withdrawal, while the lithium-related neurotoxicity findings continued. Electroconvulsive therapy (ECT) was planned for both depressive and catatonic symptoms. The Bush-Francis Catatonia Rating Scale (BFCRS), which is widely used in practice as a screening scale for catatonia symptoms (Aandi Subraniyam et al. 2020, Erdoğan et al. 2021), the maximum score of which is 69, was applied and the score was 10. Meanwhile, The HAM-D score was 25. After the symptoms of catatonia were observed, investigations were performed to exclude various probable medical causes of catatonia such as autoimmune encephalitis and rheumatological diseases. In line with this aim, limbic encephalitis panel including plasma anti-NMDA antibody, anti-nuclear antigen (ANA), anti-cyclic citrated peptide (anti-CCP), rheumatoid factor (RF), anti-double-stranded DNA (anti-dsDNA), anti-neutrophilic cytoplasmic antibody (ANCA), C3 and C4 complement levels, anti-Ro, anti-La, anti-Smith, anti-ribonucleotide

phosphorylase, anti-SCL70, HLA-B27, HLA-B51 tests were performed. No pathological value was detected in the laboratory tests.

After eleven sessions of bitemporal ECT, both depression and catatonia symptoms improved. The scores of HAM-D and BFCRS were calculated as 1 and 0, respectively. After ECT sessions were terminated, lamotrigine treatment was started and the dose was increased up to 200 mg/d. While the patient was discharged with complete remission of depressive symptoms, ataxic gait and tremor in both hands continued in a less severe form. In her examination four months after her discharge, it was observed that her mood was euthymic, her neurological examination was normal, and the impairment in her neuropsychological tests had improved.

The results of the neuropsychological tests applied to the patient during the clinical follow-up period, along with the score, Z-score and evaluation interpretation are shown in Table-1.

DISCUSSION

This article presents a case with catatonia symptoms occurring during neurotoxicity due to chronic lithium use. On the third day of hospitalization, disorientation, severe extrapyramidal and cerebellar symptoms emerged while using olanzapine 10 mg/d, sertraline 25 mg/d and lithium 300 mg on alternate days.

Infectious diseases, idiopathic normal pressure hydrocephalus (NPH), neuroleptic malignant syndrome (NMS), and lithium neurotoxicity were considered in the differential diagnosis of the condition in which delirium and neurological symptoms appeared together, along with a fever of 37.8°C. Infectious factors were excluded because no abnormal findings were detected in laboratory tests, the physical examination was normal, and the Covid-19 PCR test was negative. The diagnosis of lithium neurotoxicity was confirmed, moving away from the diagnosis of NMS due to the absence of any laboratory findings to support NMS, the spontaneous improvement of fever in a short time, the absence of lead pipe rigidity, and autonomic instability symptoms, and emergence and persistence of cerebellar symptoms.

Normal Pressure Hydrocephalus (NPH) had also been considered in the differential diagnosis, taking into account the presence of the ataxic gait and cognitive dysfunction in neurological examination. Normal-pressure hydrocephalus, also known as Hakim-Adams syndrome, is a clinical condition presenting with symptoms such as enlargement of the ventricles, urinary incontinence, gait disturbance and cognitive impairment (Oliveira et al. 2019) and named as idiopathic NPH, if it does not develop secondary to any underlying cause. The patient's ataxic gait was not observed at the time of admission to the inpatient clinic. It occurred simultaneously with other neurological symptoms during the course, and was not in the magnetic gait style that is usually characteristic of normal pressure hydrocephalus (Fraser and Fraser 2007). Besides the observations presented above, the ventricles were found to be normal in width in the brain MRI, there was no accompanying urinary incontinence, and neuropsychological tests and other neurological findings completely resolved after lithium was discontinued and did not reappear.

In the clinical condition of lithium neurotoxicity, changes in consciousness; cerebellar symptoms such as ataxia, dysarthria, dysmetria, intentional tremor; neuromuscular excitability in the form of extrapyramidal manifestations, irregular and coarse tremor, fasciculations, myoclonic beats; impairment in cognitive and executive functions, prolonged seizures and status epilepticus can be seen (Baird-Gunning et al. 2017, El Balkhi and Mégarbane 2017). Catatonia, albeit rarely, can be seen as a manifestation of lithium neurotoxicity. When the literature is reviewed, it is seen that two catatonia cases related to lithium neurotoxicity have been reported so far (Desarkar et al. 2007, Medda et al. 2018). The first case report is about a 16-year-old female patient diagnosed with bipolar disorder and followed up with lithium treatment, who developed neurotoxicity with a serum lithium level of 2.22 mmol/L, and had catatonia symptoms such as mutism, staring, negativism, catalepsy, and stupor. In that case, it was reported that lithium treatment was discontinued. Electroconvulsive treatment was started when the serum lithium level was 2.22 mmol/L, catatonia symptoms were completely resolved with five sessions of ECT, and other neurotoxicity symptoms were completely resolved in the course (Desarkar et al. 2007). The second case is a 68-year-old female patient with bipolar disorder who developed neurotoxicity symptoms with a serum lithium level of 2.6 mmol/L. In that case, upon observing catatonia symptoms such as catalepsy, rigidity, waxy flexibility, staring, stereotypical movements, excitement and negativism, the patient's lithium treatment was discontinued and ECT was started after the serum lithium level dropped to zero. After twelve sessions of ECT, the symptoms of catatonia completely resolved, but dysarthria, ataxia, and cognitive dysfunction remained as sequelae symptoms in the following years (Medda et al. 2018). In both of these cases, signs of neurotoxicity occurred when the serum lithium level was above the therapeutic range. It has been reported that symptoms of lithium neurotoxicity may occur even when the serum lithium level is in the therapeutic range, as in our case (Arya 1996, Emilien and Maloteaux 1996, Grueneberger et al. 2009, Baird-Gunning et al. 2017, Soni 2019). The improvement of tremor, bradykinesia, postural instability, Myerson's signs, and decrease in the severity of ataxia and cogwheel rigidity after haemodialysis support the view that

Table 1. The results of the first and last neuropsychological tests, which were performed on the patient with an ınterval of four months, are shown together with the test score, z-score and ınterpretation

	First Assessment		Last Assessment	
	Score	**Z-score/Standard Deviation (SD)**	**Score**	**Z-score/Standard Deviation (SD)**
Neuropsychological Test				
Mini Mental-State Examination	24		28	
Modified Mini Mental-State Examination (3MS)	82	-1.28	91	-0.18
Clock Drawing Test	4	0.0	4	0.0
Trail Tests				
Trail-Making A Test	139	-4.05	46	-0.6
Trail-Making A Correction Number	1	-5.88	0	0.0
Trail-Making B Test	259	-4.56	114	0.1
Trail-Making B Correction Number	0	0.0	0	0.0
Trail Making B+A Score	398	-4.46	160	-0.17
Trail Making B-A Score	120	-2.44	68	0.5
Digit Span Memory Tests				
Digit Span Test: Total	8	Between -1 SD and -2 SD	9	Between 0 SD and -1 SD
Digit Span Test: Forward	5	Between 0 SD and -1 SD	5	Between 0 SD and -1 SD
Digit Span Test: Backward	3	Between 0 SD and -1 SD	4	Between 0 SD and -1 SD
Verbal Fluency Tests				
Verbal Fluency Test (Letter-S)	8	-1.45	17	1.11
Verbal Fluency Test (Letter-A)	6	-1.45	12	0.05
Verbal Fluency Test (Letter-Z)	8	-0.14	9	0.28
Semantic Fluency Tests				
Semantic Fluency Test (animal)	11	-1.95	15	-1.23
Semantic Fluency Test (human)	16	-1.84	21	-1.06
Semantic Fluency Test (animal-human)	16	-0.79	17	-0.54

Overall, the mild impairment in the general cognitive performance, executive functions and complex attention of the patient, which was detected in the first evaluation, have improved in the final evaluation (Ayhan et al. 2022).

the neurological symptoms seen in this patient are related to lithium neurotoxicity.

Although catatonia is a syndrome that may occur during mood episodes, no signs of catatonia were detected during any mood episode in the past course of this patient and during her last depressive episode. Catatonic symptoms emerged in our patient for the first time just after the development of lithium neurotoxicity. The timing of the onset of catatonia symptoms in this depressive episode and the absence of catatonia in past mood episodes support that new-emergent catatonia may be associated with lithium neurotoxicity rather than with the mood episode. However, mood disorder may have contributed to the emergence of catatonia during lithium neurotoxicity, and this condition cannot be completely excluded. As stated in another case report, catatonic symptoms were treated with lorazepam and ECT in this case as well (Medda et al. 2018). The administration of ECT while serum lithium levels are high in the central nervous system (CNS) can lead to delirium and prolonged seizures (Baird-Gunning et al. 2017, Medda et al. 2018). Therefore, in our case, the serum lithium level was dropped to zero through haemodialysis before initiating ECT.

Female gender and older age are risk factors for the development of lithium neurotoxicity (Adityanjee et al. 2005, D'Souza et al. 2011). Other risk factors are epilepsy, cognitive impairment, abnormal EEG findings (Kores and Ladder 1997), psychotic symptoms and anxiety symptoms accompanying mood symptoms in the pre-intoxication period, and the use of lithium for schizoaffective disorder

and bipolar disorder (West and Meltzer 1979). The combined use of lithium and antipsychotics increases the risk of neurotoxicity, since lithium reduces presynaptic dopamine release and antipsychotics block dopamine-2 receptors (Boora et al. 2008). In our case, the addition of olanzapine to lithium treatment was one of the risk factors that may have triggered neurotoxicity. It would be an appropriate approach to evaluate this case as acute lithium neurotoxicity developing on the basis of chronic lithium nephrotoxicity due to long-term lithium use. In our case, advanced age, female gender, diagnosis of bipolar disorder, presence of psychotic symptoms, co-diagnosis of chronic kidney disease and concomitant olanzapine use facilitated the development of lithium neurotoxicity. In this patient, haemodialysis method was used in the treatment to improve the clinical course of lithium neurotoxicity. There was a significant improvement in neurological symptoms following four haemodialysis sessions, three of which lasted six hours. In the literature, it is recommended that the duration of haemodialysis sessions be at least six hours in lithium intoxication cases (Decker et al. 2015). The approaches recommended in the literature were followed in the haemodialysis application of this case.

Serum lithium level is another determinant of lithium neurotoxicity, but it should be kept in mind that lithium neurotoxicity can also be seen in the therapeutic range. Lithium may accumulate in the brain tissue in long-term treatment, and its transition to the cerebrospinal fluid may be delayed and slow (Baird-Gunning et al. 2017). In this case, the emergence and persistence of neurotoxicity despite the discontinuation of lithium and olanzapine treatments might be related to the slow and delayed transition of lithium to the cerebrospinal fluid.

While fever may be a component of lithium neurotoxicity, it may also pose a risk for the development of neurotoxicity by stimulating protein coagulation in different parts of the CNS (Adityanjee et al. 2005). When neurotoxicity developed, there was a short-term fever response, and the accompanying confusion led to the necessity of considering infection, rheumatological diseases and NMS in the differential diagnosis. For this reason, consultations concerning the patient were conducted with the relevant departments. Infectious diseases and rheumatological diseases were excluded due to the normal results of the tests detailed in the case report section, lack of abnormal findings in the examination, and lack of family history of rheumatological diseases. The diagnosis of NMS was also excluded because the creatine kinase and leukocyte values were normal, the subfebrile fever seen in the patient spontaneously regressed within hours and was not observed again; signs of autonomic instability and lead pipe rigidity were never observed. The only type of rigidity observed in the patient was cogwheel rigidity.

The persistence of symptoms of lithium neurotoxicity two months after the discontinuation of lithium is defined as The Syndrome of Irreversible Lithium Effectuated Neurotoxicity (SILENT) in the literature (Adityanjee et al. 2005). In the review in which ninety SILENT cases were evaluated, it was reported that the number of patients whose SILENT improved within the first year after lithium discontinuation was quite low (Adityanjee et al. 2005). Ataxic gait, tremor, and cognitive impairment, which are the symptoms of neurotoxicity seen in the presented case, continued until six months after the discontinuation of lithium. It was observed that they completely recovered in the follow-up examination six months later, and thus, the presented case is one of the few SILENT cases which improved during follow-up.

In conclusion, it should be kept in mind that catatonia can be seen as one of the clinical findings of lithium neurotoxicity, albeit rarely, and that in patients on lithium therapy, if neurological symptoms that may be associated with lithium neurotoxicity, including catatonia, occur, prompt and appropriate intervention should be sought to avoid permanent neurological damage.

REFERENCES

Aandi Subramaniyam B, Muliyala KP, Suchandra HH et al. (2020) Diagnosing catatonia and its dimensions: Cluster analysis and factor solution using the Bush Francis Catatonia Rating Scale (Bfcrs). Asian J Psychiatr 52:102002.

Adityanjee, Munshi KR, Thampy A (2005) The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity. Clin Neuropharmacol 28:38-49.

Akdemir A, Örsel DS, Dağ İ et al. (1996) Hamilton depresyon derecelendirme ölçeği (HDDÖ)'nin geçerliliği- güvenirliliği ve klinikte kullanımı. Psikiyatri, Psikoloji, Psikofarmakoloji Dergisi 4:251-9

Arya DK (1996) Lithium-induced neurotoxicity at serum lithium levels within the therapeutic range. Aust N Z J Psychiatry 30:871-3.

Ayhan Y, Akbulut BB, Şişman AH et al. (2022) Psinorm: A fast, efficient and free open-source software for interpreting, reporting and archiving neuropsychological test results. Turk Psikiyatri Derg 33: 255-62.

Baird-Gunning J, Lea-Henry T, Hoegberg LCG et al. (2017) Lithium poisoning. J Intensive Care Med 32:249-63.

Boora K, Xu J, Hyatt J (2008) Encephalopathy with combined lithium-risperidone administration. Acta Psychiatr Scand 117:394-5.

D'Souza R, Rajji TK, Mulsant BH et al. (2011) Use of lithium in the treatment of bipolar disorder in late-Life. Curr Psychiatry Rep 13:488-92.

Decker BS, Goldfarb DS, Dargan PI et al. (2015) Extracorporeal treatment for lithium poisoning: Systematic review and recommendations from the extrip workgroup. Clin J Am Soc Nephrol 10:875-87.

Desarkar P, Das A, Das B et al. (2007) Lithium toxicity presenting as catatonia in an adolescent girl. J Clin Psychopharmacol 27:410-2.

El Balkhi S and Mégarbane B (2017) Lithium toxicity: Clinical presentations and management. Editörler: Malhi GS, Masson M,Bellivier F. The Science and Practice of Lithium Therapy. Cham: Springer International Publishing, p. 277-92.

Emilien G, Maloteaux JM (1996) Lithium neurotoxicity at low therapeutic doses hypotheses for causes and mechanism of action following a retrospective analysis of published case reports. Acta Neurol Belg 96:281-93.

Erdogan IM, Aytulun A, Avanoglu KB et al. (2022) Bush Francis Katatoni Değerlendirme ve KANNER Katatoni Ölçeklerinin Türkçe Uyarlama, Geçerlik ve Güvenirlik Çalışması. Türk Psikiyatri Derg https://doi.org./10.5080/u27064 (in press).

Fraser JJ and Fraser C (2007) Gait disorder is the cardinal sign of normal pressure hydrocephalus: A case study. J Neurosci Nurs 39:132-4.

Grueneberger EC, Maria Rountree E, Baron Short E et al. (2009) Neurotoxicity with therapeutic lithium levels: A case report. J Psychiatr Pract 15:60-3.

Kores B and Lader MH (1997) Irreversible lithium neurotoxicity: An overview. Clin Neuropharmacol 20:283-99.

Malhi GS, Gessler D, Outhred T (2017) The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. J Affect Disord 217:266-80.

Medda P, Socci C, Toni C et al. (2018) Neurological deficits after lithium intoxication in a bipolar woman with catatonia treated with ECT. J Clin Psychopharmacol 38:405-7.

Oliveira LM, Nitrini R, Román GC (2019) Normal-pressure hydrocephalus: A critical review. Dement Neuropsychol 13:133-43.

Soni S (2019) Lithium neurotoxicity presenting as dementia with therapeutic serum lithium levels. BMJ Case Rep 12.

West AP and Meltzer HY (1979) Paradoxical lithium neurotoxicity: A report of five cases and a hypothesis about risk for neurotoxicity. Am J Psychiatry 136:963-6.