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Clinical, laboratory and neurological assessment of lithium toxicity in patients with bipolar disorders

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ABSTRACT

Background: Lithium was once the drug of choice for treating bipolar disorder. It has a low therapeutic efficacy and frequently appears in hazardous concentrations in clinical practice. It has been found that long-term lithium intoxication, which is caused by lithium gradually building up, is more common. The overwhelming majority of the symptoms are neurological; commonly, the mental state is disturbed and could even become coma-like.

Aim: To measure the clinical, laboratory, and neurological changes of lithium toxicity in patients with bipolar disorder in correlation with these effects with periodic lithium level monitoring.

Methods: In order to pinpoint individuals with euthymic BD based on various serum concentrations (<1.2, 1.2-3, and >3 mmol/L), the cohort research was carried out in Al Azhar New Damietta Hospital from September 1, 2022 to the end of January 2023. Disease was confirmed using the Young Mania Rating Scaling (YMRS) and the structured diagnostic examination for DSM-V axis I disorders. Demographic, clinical, and laboratory data were obtained for analysis.

Results: The distribution of severe/moderate/mild neurological symptoms for the >3 mmol/L, 1.2–3 mmol/L and <1.2 mmol/L groups were 0/10/40, 10/15/10 and 20/0/0 % respectively ($p < 0.05$). Cardiovascular symptoms appeared more common in patients receiving >3 mmol/L of lithium than those receiving 1.2–3 mmol/L and <1.2 mmol/L of lithium level (10% versus 5 and 0%, respectively $p < 0.05$). The blood urea nitrogen, creatinine and TSH levels significantly increased in severe toxic lithium level (>3 mmol/L, $p<0.05$).

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Conclusion: Participants receiving continuous lithium treatment should be closely watched for its toxicity and administered right away in the event of poisoning due to the outstanding results of detoxification programs.

Keywords: *Bipolar disorder, lithium, toxicity, neurological symptoms*

INTRODUCTION

Repeated manic or hypomanic episodes that alternated with periods of no complaints characterize bipolar disorder (BD), a severely and chronic mental condition (1). As up to 20 to 50 percent of treated individuals do not adequately react to maintenance therapy, investigation into the psychopharmacology of BD is still ongoing (2, 3). In this regard, a crucial first step towards that tailored approach to BD is the discovery of indicators that reveal details about the current state of disease and the anticipated pharmaceutical reaction (4). Lithium is both the most successful long-term treatment for unipolar depression and bipolar illness. But there have been worries about its efficacy. A lower therapeutic index applies to lithium. Clinical practice routinely encounters toxic levels (5).

Lithium's mechanism of action is not well known. It works at additional signalling pathways besides neurotransmitter receptors. Lithium interacts with down - stream signaling pathways cascades, such as the inhibitory activity of GSK-3 (glycogen synthases kinases 3) and proteins kinases C 3, to regulate genes expressions for growth factors as well as neuronal plasticity (6). This contains second messengers, like the phosphatidyl inositol structure, in which lithium inhibits the enzymatic inositol monophosphatases, affects G proteins, and restricts genes expressions (7). According to some writings, lithium is a component that functions in the body similarly to sodium (8). Throughout the human body, sodium is a component of numerous biochemical functions. According to some research, bipolar patients have greater intracellular sodium and calcium contents than healthy individuals. These amounts are reportedly reduced by lithium (9).

Since the therapeutic opportunity for lithium is small, it is necessary to routinely check the plasma medication contents. Between 0.8 and 1.2 mmol/L8 of lithium are considered therapeutic levels (10). Above 1.5 mmol/L, lithium becomes poisonous. Diarrhea, nausea and anorexia, and are gastrointestinal and CNS consequences of lithium poisoning (muscle twitching, diarrhea, nausea and anorexia), respectively (11, 12). Seizures and disorientations can happen at levels higher than 2 mmol/L, and these conditions can lead to coma and death. According to one study, lithium toxicity is associated with a 9% fatality rate and a 10% chance of patients developing chronic neurological damage (13). Osmotic or forceful alkaline diuresis must be utilized in the occurrence of more severe symptoms; however, thiazides or looping diuretics cannot be used as they may interfere negatively with lithium (14). Individuals who are taking lithium must be educated about toxicity symptoms and factors associated (15).

There are three popular methods of lithium intoxication: acute toxicity in patients who have never received lithium, which happens when a patient intentionally consumes large doses of the drugs while trying to commit suicide or unintentionally overdose deaths, acute-on therapeutic from acute ingestion while obtaining lithium therapies, and chronic lithium toxicity (16). The most typical form was discovered to be chronic lithium poisoning. Chronic lithium toxicity develops when there are progressive accumulations of lithium, which is typically caused by renal impairment, medication combinations with angiotensin-converting enzymes inhibitors or diuretics, volumes depletions, and concomitant diseases such congestive heart failure or cirrhosis (17). Lithium medication has significant adverse effects called neurotoxicity. Both lithium monotherapy with standard blood values or with toxic levels as well as combination therapy with other medications, especially with antipsychotics or antidepressants, have been recorded for it (18).

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Lithium neurotoxicity could even be seen at therapeutic blood levels and could be either reversible or irreversible. Extremity dyscoordinations and tremors are symptoms of acute lithium poisoning, which first affects fast-acting neurons governing coordination (19). Progressive development of slurred speech, muscle fasciculation, seizures, nystagmus, and extrapyramidal characteristics may be brought on by growing toxicity. Delirium and obtundations in acute neurotoxicity could be additional symptoms (20).

Although prolonged blood lithium levels > 1.5 mEq/L might well be correlated with a risk of toxicity, they might not be regularly higher enough to cause nerve damage (21). Consistent levels > 2.5 mEq/L sometimes result in neurologic side effects, particularly convulsions and cerebellar dysfunction (22).

Medical trials have shown that lithium has a permanent neurotoxic effect. A lasting aftereffect of intoxications, the condition of irreversible lithium-effectuated neurotoxicity manifests as ongoing cerebellar impairment. Additional major neurologic issues can be seen (23). Dystaxia and dysarthria are brought on by demyelination, which mostly affects the cerebellum but also happens elsewhere. Permanent malfunction of the cerebellum and pyramidal cells may follow (24). Through a hospital-based cross-sectional research published over a four-year period at the Poisoning Control Center University, the report's objective was to assess the neurotoxicity amongst lithium-intoxicated individuals and its relationship to serum lithium contents. There are certain things that can alter how lithium-toxic individuals turn out (25).

SUBJECTS AND METHODS

Study type and setting

This was a cross sectional prospective study carried out at Al-Azhar New Damietta Hospital during the period from September 1, 2022 to the end of January 2023.

Subjects

The study included 50 patients diagnosed as bipolar disorder and treated with lithium. Medical history, careful physical examinations including: renal, gastrointestinal, pulmonary diseases, cardiovascular, neurological, any toxic sings and complete investigations of patients were obtained upon enrollment into the study. Investigators noted down important and detailed information of all the patients, like their age, and sex as well as their patient code, in-patient or outpatient admission status and medical service type. At present, the status of electrolytes, renal and liver function values were evaluated at the same time of estimating the Lithium level. Important laboratory tests and investigations such as blood urea nitrogen, serum creatinine concentration, TSH, serum total calcium both serum ALT and AST levels were conducted.

Inclusion criteria

This research consisted adult patients over 20 years old who have been receiving lithium medication and had no epileptic symptoms.

Exclusion criteria

Exclusion criteria for the study included those under the age of 18, those who already had hepatic impairment, and those who were using multiple antiepileptic medications, with neuroleptic malignant disorders, metabolic causes of changed level of consciousness, pathophysiologic neurological issues as demonstrated by altered brain CT and/or MRI observations (the absence of stiffness and normal serum creatine kinase govern this out).

Data collection

Subjects were divided into three groups based on their serum lithium levels as following:

Group A: Individuals whose serum lithium values are less than 1.2 mmol/L.

Group B: Individuals whose serum lithium values are 1.2 - 3 mmol/L.

Group C: Individuals whose serum lithium values are more than 3 mmol/L.

Lithium level was analyzed with flame emission spectrophotometry, a method that shows excellent precision and accuracy (1) by using a Beckman Coulter SynchronCX7 system (Brea, CA, USA), colorimetric assay. The normal therapeutic range was 0.61.2 mEq/L with minimum effective concentration 0.6, trough concentration 1-1.2 and value more than 1.5

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mmol/L twelve hours after dosage indicate significant risk for intoxication. Serum lithium was determined as a trough at steady state, ie, 5 days after initiation of the drug.

Lithium was started or the dosage was changed within an hour before the test period for lithium serum level and at minimum three days thereafter. Subjects' BD-related properties were analyzed, and they comprised age, sex, and clinical characteristics (renal, gastrointestinal, pulmonary diseases, cardiovascular, neurological); and concurrent medicines (antipsychotics, antidepressants and lamotrigine drugs).

Patients are diagnosed as bipolar disorder by:

Clinical interview , depending on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM V) (27)

the Structured Clinical Interview for Diagnosis (SCID) scale (26)

overall Young Mania Rating Scale (YMRS) scoring of less than ≥15 to participate in the therapeutic experiment at the beginning of the research and on a 3-months regular basis thereafter (28).

Blood chemistries were analyzed by Dimension® RxL-Max® Integrated Chemistry System (Siemens Healthcare Diagnostics).

The recurring of any severe mood episodes, which had been characterized as the happening of psychiatric hospitalization or any modifications, was the end measure of treatment effectiveness (Boost the original medication's dose or incorporate additional medication) while taking psychotropic drugs (Antidepressants, antipsychotic drugs, and mood stabilizers (lithium, carbamazepine, lamotrigine, and valproate). These factors have already been described in related investigations (29-32). All enrolled subjects were monitored from the index date (the lithium serum levels testing date) to the date the result occurred.

Ethical consideration

The Ethical Committee and Al-Azhar New Damietta Hospital gave their permission. The participants' or their family' written informed consents were acquired. They received guarantees that whatever data they gave would be preserved completely private and anonymously. The study was designed to follow the declaration of Helsinki.

METHODS

Statistical Analysis

The statistical software SPSS (Statistical Package for the Social Science), version 26, was employed. The qualitative results were compared using the Chi-square test, whereas the unpaired t test was utilized to evaluate the quantitative data between the three groups. At $P< 0.05$, it was declared significant. The threshold for highly significance was set at $P <0.001$.

RESULTS

Basic features of the patient population

A sum of 50 respondents from this cohort were monitored and split into three groups based on their lithium serum levels: <1.2 mmol/L (20 instances, mean ± SD 0.30 ± 0.06 mmol/L), 1.2-3 mmol/L (20 instances, 1.55 ± 0.11 mmol/L), and >3 mmol/L (10 instances, 3.86 ± 0.06 mmol/L). The features of the individuals who are a part of this sample are summarized in Table 1. The respondents' mean age was 42 years, and the majority frequently experienced concomitant hypertension (8%) and were taking antipsychotic drugs (74%). The average age at which bipolar indications first appeared was 26.06 ± 13.5a years. In total 50 instances, the average age at the beginning of depression was 25.06 ± 8.1years. The DICA-R revealed that 44% of people displayed psychotic characteristics. Oppositional defiant disease (100%), attention deficit hyperactivity disorder (74%), separation anxiety disorder (26%), conduct disorders (36%), and obsessive-compulsive disorders (16%) were all extremely common forms of comorbidities. Throughout the course of the trial, antipsychotics (74%) and antidepressants (36%) were administered concurrently (Table 1).

TABLE 1: General characteristics together with patients' lithium group.

Characteristics	>3 mmol/L (n = 10)	1.2–3 mmol/L (n = 20)	<1.2 mmol/L (n = 20)	Total (N = 50)	p-value
Gender					0.001
Female	6 (60)	7 (35)	9 (45)	22 (44)	
Male	4 (40)	13 (65)	11 (55)	28 (56)	
Age, year	41.86 ± 15.98	43.21 ± 14.88	40.52 ± 14.70	42.25 ± 14.90	0.664
Characteristics of mania					
Manic/hypomanic episodes	13.24 ± 0.964	11.42 ± 2.48	10.31 ± 1.47	12.762 ±1.3	0.08
Mean duration of illness (years)	4.14 ± 2.33	4.52 ± 1.54	4.11 ± 0.99	4.36 ± 2.5	0.334
Onset of depression prior to mania	2 (20%)	5 (25%)	7 (35%)	14 (28%)	0.04*
Age of onset of depression (years)	24.11 ± 11.54	19.18 ± 6.954	26.45 ± 11.55	25.06 ± 8.1a	0.087
Age of onset of mania (years)	31.42 ± 8.27	26.14 ± 15.21	16.31 ± 7.14	26.06 ± 13.5a	0.158
Neuroleptic-naïve	4 (40%)	13 (65%)	15 (75%)	32 (64%)	0.066
Bipolar disorder	10 (100%)	20 (100%)	20 (100%)	50 (100%)	1
Mixed presentation	7 (70%)	13 (65%)	16 (80%)	36 (72%)	0.118
Psychotic	5 (50%)	7 (35%)	10 (50%)	22 (44%)	0.075
First episode7	3 (30%)	2 (10%)	6 (30%)	11 (22%)	0.079
Diagnosis					
Disruptive behavioral disorders					0.165
Conduct disorder	3 (30%)	5 (25%)	10 (50%)	18 (36%)	
Attention deficit disorder	5 (50%)	15 (75%)	17 (85%)	37 (74%)	
Oppositional defiant disorder	10 (100%)	20 (100%)	20 (100%)	50 (100%)	
Anxiety disorders					0.245
Avoidant	0 (0%)	4 (20%)	3 (15%)	7 (14%)	
Obsessive-compulsive disorder	2 (20%)	3 (15%)	3 (15%)	8 (16%)	
Two or more comorbid anxiety disorders	2 (20%)	3 (15%)	8 (40%)	13 (26%)	
Psychosis	1 (10%)	2 (10%)	7 (35%)	10 (20%)	0.38
Other					
Bulimia	0 (0%)	0 (0%)	1 (5%)	1 (2%)	
Encopresis	1 (10%)	1 (5%)	2 (10%)	4 (8%)	
Enuresis	3 (30%)	2 (10%)	2 (10%)	7 (14%)	
Medications					0.001
Antipsychotics	8 (80%)	15 (75%)	20 (100%)	37 (74%)	
Antidepressants	2 (20%)	6 (3%)	10 (5%)	18 (36%)	
Lamotrigine	1 (10%)	2 (10%)	1 (5%)	4 (8%)	

Data were presented as means ± standard deviations or N (percent).

Table 2 showed lithium toxicity symptoms

among the studied groups. It was noticed that mild symptoms appeared most among patients received 1.2–3 mmol/L of lithium (30%) However, moderate and severe intoxication indicators were found most among patients received >3 mmol/L of lithium (30 and 60% respectively).

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TABLE 2: Severity of lithium toxicity symptoms degree among the studied groups

	>3 mmol/L (n = 10)	1.2–3 mmol/L (n = 20)	<1.2 mmol/L (n = 20)	Total (N = 50)	p-value
Mild symptoms	1 (10%)	6 (30%)	3 (15%)	10 (20%)	<0.001*
Nausea	0 (0%)	1 (5%)	0 (0%)	1 (2%)	<0.001*
Vomiting	1 (10%)	2 (10%)	0 (0%)	3 (6%)	<0.001*
Lethargy	0 (0%)	1 (5%)	1 (5%)	2 (4%)	<0.001*
Tremor	0 (0%)	1 (5%)	0 (0%)	1 (2%)	<0.001*
Fatigue	0 (0%)	1 (5%)	2 (10%)	3 (6%)	<0.001*
Moderate intoxication	3 (30%)	5 (25%)	2 (10%)	10 (20%)	<0.001*
Confusion	0 (0%)	2 (10%)	1 (5%)	3 (6%)	<0.001*
Agitation	0 (0%)	1 (5%)	0 (0%)	1 (2%)	<0.001*
Delirium	1 (10%)	0 (0%)	0 (0%)	1 (2%)	<0.001*
Tachycardia	1 (10%)	1 (5%)	0 (0%)	2 (4%)	<0.001*
Hypertonia	1 (10%)	1 (5%)	1 (5%)	3 (6%)	<0.001*
Severe intoxication	6 (60%)	5 (25%)	0 (0%)	11 (22%)	<0.001*
Coma	1 (10%)	2 (10%)	0 (0%)	3 (6%)	<0.001*
Seizures	2 (20%)	1 (5%)	0 (0%)	3 (6%)	<0.001*
Hyperthermia	2 (20%)	1 (5%)	0 (0%)	3 (6%)	<0.001*
Hypotension	1 (10%)	1 (5%)	0 (0%)	2 (4%)	<0.001*
Total	10 (100%)	16 (80%)	5 (25%)	31 (62%)	<0.001*

*p significant if <0.05

Table 3 and figure 1 demonstrates that neurological symptoms following lithium intoxication appeared to predominate. Individuals with high lithium intoxication (>3 mmol/L) experienced more severe neurological symptoms than those with mild and moderate intoxication (<1.2 and 1.2-3 mmol/L), according to the severity of their complaints. The distribution of mild/moderate/severe neurological symptoms for the >3 mmol/L, 1.2–3 mmol/L and <1.2 mmol/L were 0/10/40, 10/15/10 and 20/0/0 % respectively ($p< 0.05$). In addition, cardiovascular involvements and renal diseases were more common in patients receiving >3 mmol/L severe lithium poisoning than those receiving 1.2–3 mmol/L and <1.2 mmol/L (10% versus 5 and 0% in cardiovascular disease and 20, 10 and 0% for renal diseases respectively $p < 0.05$).

TABLE 3: Clinical signs of the study participants, grouped by blood lithium levels (N = 21)

Characteristics	>3 mmol/L (n = 10)	1.2–3 mmol/L (n = 20)	<1.2 mmol/L (n = 20)	p-value
Renal, n (%	2 (20%)	2 (10%)	0 (0%)	0.031*
Gastrointestinal, n (%)	1 (10%)	4 (20%)	0 (0%)	0.072
Pulmonary diseases, n (%)	1 (10%)	2 (10%	1 (5%)	0.203
Cardiovascular, n (%)	1 (10%)	1 (5%)	0 (0%)	0.018*
Neurological, n (%)	5 (50%)	7 (35%)	4 (20%)	0.501
Severity of neurological symptoms:				0.022*
Severe, n (%)	4 (40%)	2 (10%)	0 (0%)	
Moderate, n (%)	1 (10%)	3 (15%)	0 (0%)	
Mild, n (%)	0 (0%)	2 (10)	4 (20%)	

*P significant if <0.05

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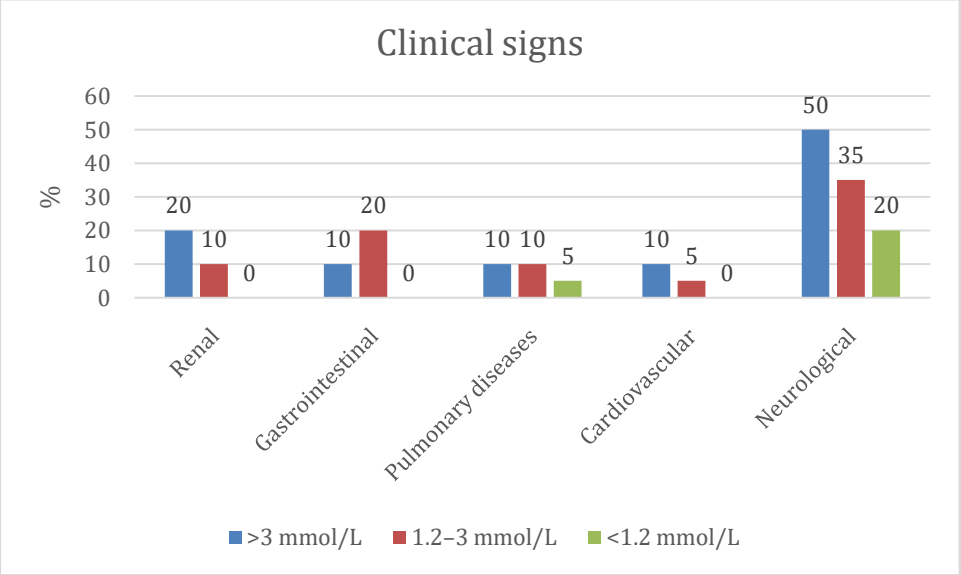

FIGURE 1: Clinical sign among the studied cases

Table 4, figure 2 and 3 also shows that patients with severe lithium poisoning (>3 mmol/L group) suffered greater degrees of renal impairment than patients with mild and moderate poisoning (<1.2 and 1.2-3 mmol/L groups). The blood urea nitrogen and creatinine levels of the severe (>3 mmol/L) group versus mild and moderate groups (<1.2 and 1.2-3 mmol/L) were 27.1 ± 17.8 mg/dL/1.85 ± 1.26 versus 14.1 ± 7.16/1.30 ± 0.64 mg/dL and 14.5 ± 6.31/ 1.25 ± 0.55 mg/dL, respectively ($p < 0.05$). TSH level increased among the >3 mmol/L (7.3 ± 0.657) group than in other groups with a statistically significant difference ($p<0.001$).

TABLE 4. Laboratory data of study patients, stratified according to blood lithium level (N = 21)

Characteristics	>3 mmol/L (n = 10)	1.2–3 mmol/L (n = 20)	<1.2 mmol/L (n = 20)	p-value
Calcium (mg/dL)	10.3 ± 0.86	9.33 ± 0.85	9.29 ± 0.94	0.863
Potassium (mEq/dL)	4.3 ± 0.42	3.96 ± 0.70	3.88 ± 0.99	0.338
Sodium (mEq/dL)	140 ± 3.45	140 ± 3.33	138 ± 4.59	0.543
Creatinine (mg/dL)	1.85 ± 1.26	1.30 ± 0.64	1.25 ± 0.55	0.002*
Urea nitrogen (mg/dL)	27.1 ± 17.75	14.1 ± 7.16	14.5 ± 6.31	0.002*
Platelet count (x103 per mL)	256 ± 105.7	262 ± 59.2	264 ± 66.3	0.114
Neutrophils (%)	73.6 ± 11.5	76.8 ± 7.2	75.5 ± 1.5	0.088
White blood cell count (per mL)	8700 ± 3802	11141 ± 4199	11155 ± 3099	0.861
Hemoglobin (g/dL)	12.6 ± 1.61	11.9 ± 0.98	11.3 ± 0.11	0.062
TSH level**mU/l**	7.3 ± 0.657	4.455± 0.166	2.56 ± 0.024	<0.001*

*P value significant if <0.05.

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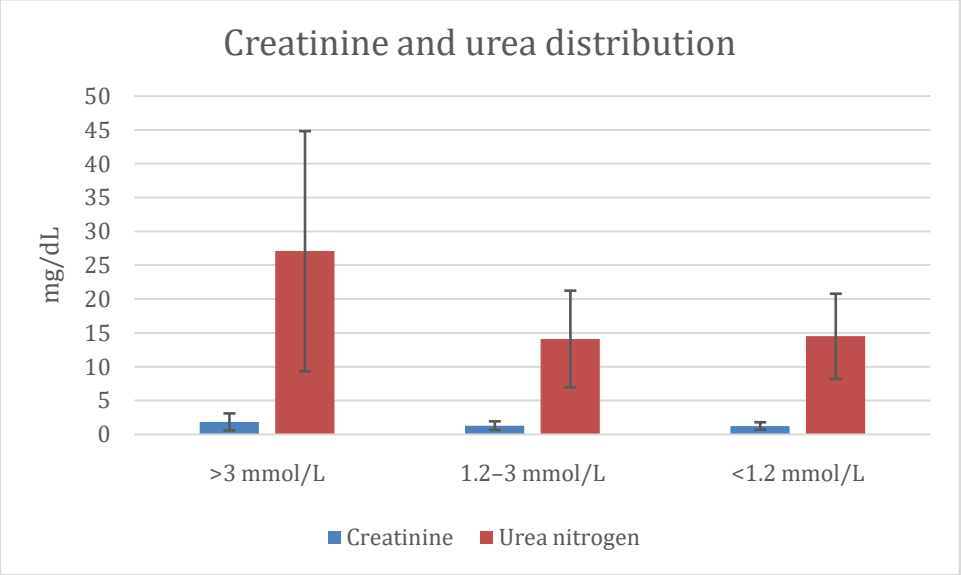

FIGURE 2: Creatinine and urea distribution among the studied cases

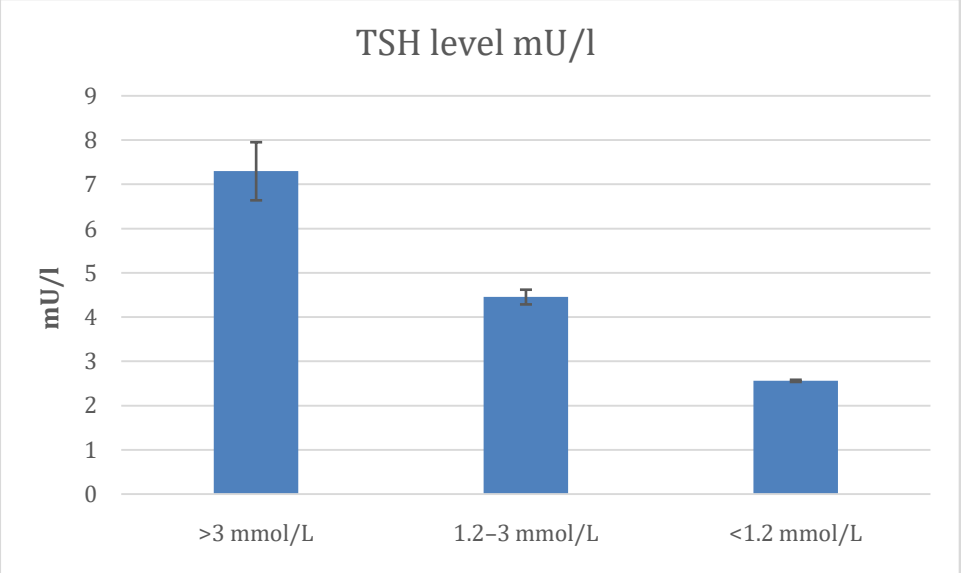

FIGURE 3: TSH level among the studied cases

DISCUSSION

This retrospective cohort study examined the toxicity level of various lithium serum ratios for the prevention of mood episodes of any polarity in patients with BD receiving maintenance therapy. Those with blood lithium contents more than 3 mmol/L showed a significantly toxicity symptoms incidence and a significant change in clinical, neurological and laboratory findings than those with values beneath 1.2 mmol/L and 1.2-3 mmol/L.

In our investigation, toxicity and serum lithium content were associated ($p<0.0001$). This is consistent with recent research that indicated that extreme toxicity was more likely to occur at greater lithium levels (33, 34). The brain-to-serum lithium concentration ratio is also said to vary significantly between individuals, which could make certain individuals more vulnerable (35).

Hemodialysis, in contrast, was successful in eliminating lithium ions from poisoned individuals, with a mortality rate of 8.6% (36).

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Hemodialysis was determined to be required in a survey of 68 British individuals by Dyson et al. (37) when renal insufficiency was existent and when serum lithium levels were extremely higher or growing quickly (37). 55 American individuals with lithium intoxication were included in the study by Gadallah et al (38). Ten of the 42 with acute poisoning had blood lithium levels greater than 3.5 mEq/L, and five received hemodialysis treatment.

We have shown that renal disease, gastrointestinal abnormalities. Individuals who use lithium regularly have respiratory, cardiovascular, and neurological conditions, and those who acquire lithium toxicity do so more commonly. Current NICE guidelines for the management of bipolar disease (39) The Royal College of Psychiatrists has implemented the current NICE recommendations for the treatment of bipolar disorder, which advise monitoring plasma lithium rate every six months in stable patients and every three months in increased risk patients, such as elderly patients, those taking medications that interact with lithium, individuals with poorer compliance, and individuals whose most recent plasma lithium amount was ≥0.8 mmol/l. In latest days, comprehensive monitoring for negative effects among individuals on lithium has received more attention (40).

It is crucial to distinguish between data relating to the effects of lithium dosage and lithium poisoning when evaluating the effects of lithium on renal functions. Our study revealed that renal diseases were more common in patients receiving >3 mmol/L severe lithium poisoning than those receiving 1.2–3 mmol/L and <1.2 mmol/L. The implications of long-term lithium on kidney function were thoroughly examined in the initial formal meta-analysis by Knight et al (41), It discovered that the probability of end stage kidney failure is lower and that there is limited indications for a clinically meaningful decline in renal function in the majority of individuals. The exclusions of individuals who had a history of lithium toxicity (in several trials) and the lack of adequate data to identify these people or relate the clinical manifestations to the number of instances of toxicity were, though, weaknesses of this meta-analysis. According to a recent large retrospective cohort study conducted by Shine et al., stage 3 CKD was substantially related with the occurrence of lithium toxicity (42).

Chronic tubulointerstitial nephropathy seems to serve as the pathogenesis of persistent lithium-induced renal damage (43, 44). It has been shown that the time and cumulative doses of lithium are associated to the severity of interstitial fibrosis on kidney biopsy (45). According to one research, people who have been exposed to lithium chronically for longer than 18 years may experience an irreparable impairment (46). This could also be due to secondary glomerulosclerosis brought on by diabetes and cardiovascular disease which are more common in people with bipolar disorder than in the normal community (47).

The current study revealed that the blood urea nitrogen and creatinine levels of the severe poisoning group (>3 mmol/L) versus mild and moderate poisoning groups (<1.2 and 1.2-3 mmol/L) differed significantly. Although it is essential to track renal functionality in individuals taking lithium administration, this may not always happen in clinical settings. 40% of individuals using lithium over a 7-year duration from 1997 to 2004 did not have their serum creatinine values taken, according to a sizable French research (48). In contrary, all participants in our study had their serum creatinine levels tested.

A recently population-based cohort analysis of 1120 respondents reported no evidence of a relationship between the change rate of eGFR over time and stable lithium medication (lithium contents within the recommended range) (49). When compared to individuals with lithium values within the healthy range, we found that patients with toxic lithium amounts had a greater frequency of renal impairment (1.85 ± 1.26; $P < 0.05$).

It is generally known that acute lithium intoxication can cause neurotoxicity. The present study found that patients with severely lithium intoxication (>3 mmol/L) experienced more severe neurological problems than those with mild and moderate toxicity (<1.2 and 1.2-3 mmol/L, respectively). Over

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than 100 instances of lithium neurotoxicity have been documented thus far (50). Traditionally, it was believed that lithium-associated neurotoxicity was transitory; unfortunately, Cohen and Cohen's 1976 publication of irreparable brain damage linked to the combination of lithium and haloperidol raised awareness of the danger of irreversible brain damage linked to lithium (51). Traditionally, it was believed that lithium-associated neurotoxicity was transitory; unfortunately, Cohen and Cohen's 1976 publication of irreparable brain injury linked to the combination of lithium and haloperidol raised awareness of the danger of irreversible brain damage linked to lithium (52), Lower serum lithium values are in agreement with intracellular accumulation. Therefore, even when serum lithium values were within the recommended range, neurological symptoms could increase (53).

Little focus has been paid on the correlation with other metabolic and endocrine abnormalities, even if recent papers have concentrated on the hazard of renal dysfunction in individuals undergoing lithium medication. The incidence of changes in thyroid and calcium homeostasis was also examined. Lithium is reported to have a variety of effects on thyroids function, including goitre, hypothyroidism, and associations with both thyroid autoimmunity and hyperthyroidism (54). Lithium inhibits thyroid hormone secretion, which is a crucial thyroidal activity (55), in both euthyroid and hyperthyroid sufferers. There is no proof that discontinuing lithium will result in the thyroids function in this group returning to normal. Lithium's immunological effects on thyroids antibodies levels may speed up the development of thyroids autoimmunity.

Lithium is considered to cause hyperparathyroidism by inactivating the calcium detection receptors and interfering with intracellular second messenger transmission, which causes the calcium-PTH curve's set-point to move to the right and diminish the parathyroid gland's sensitivity to serum calcium levels (56). There is contradicting information regarding how lithium affects the levels of serum calcium and parathyroid hormone (PTH). About 12–25% of individuals, cross-sectional investigations of hypercalcaemia and hyperparathyroidism linked to lithium indicate increased PTH and/or serum calcium above the standard recommended ranges (57-59). Assessments of the incidence of primary hyperparathyroidism in the wider population range from one to seven instances per 1,000 persons (60, 61). The long-term effects of lithium-induced hypercalcaemia are undetermined, and the majority of individuals have mild, asymptomatic hypercalcaemia(62). Due to the varied character of the studies examined, there have been inconsistent findings concerning how lithium affects calcium metabolism (63, 64). The main limitations include the small sample size. In addition, the study had a retrospective bias.

CONCLUSION

Those with serum concentrations >3 mmol/L in our retrospective cohort of patients with bipolar disorder (BD) receiving lithium maintenance therapy had a significantly higher risk of toxicity symptoms cardiovascular, renal and neurological dysfunctions. Awareness and familiarity with all neurological, possible endocrine, and renal issues that demand observation in individuals receiving this medicine are crucial given all these elements of lithium usage. Since there are few successful treatment options for bipolar affective disorder, discontinuing lithium medication can be difficult for several individuals. Proper tracking is required to spot potential problems and start early and effective therapy.

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