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Unrecognized acute lithium toxicity: a case report

Case Report

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Abstract: We report a case of a 63-year-old male who has been admitted to the Emergency department with nonspecific symptoms. Lithium toxicity was not at first recognized. When we obtained sufficient information about previous medication and medical history, we measured lithium levels found to be 1.46 mmol/L. Although the value of lithium was mildly elevated, nephrotoxicity was produced leading to severe renal insufficiency and neurological symptoms. Hemodialysis was started, and we succeed to treat the patient without squeals. This case illustrates some of the factors that lead to lithium toxicity as well as the need to consider lithium toxicity to the differential diagnosis of a patient presenting with renal insufficiency with or without change in mental status and neurologic symptom.

Keywords: *Lithium toxicity • Dehydration • Hemodialysis*

1. Introduction

Lithium has been used in medicine since the 1860s [1]. For many years, lithium was used as an efficient drug in treating manic episode of bipolar affective disorder [2-5]. Multiple mechanisms of lithium have been described [5,6].

Lithium is very quickly resorbed from the gastrointestinal tract and quickly diffuses to liver and kidneys. Approximately, 60-70% is absorbed in proximal tubules, while there is doubt about reabsorption in distal tubules [7,8]. Studies suggest it is reabsorbed in proximal tubules with the same transporter as Na+; which is why lithium is being reabsorbed much more in case of hyponatremia, which can lead to intoxication. Quite opposite occurs with hypernatremia.

In a mechanism of toxic action, lithium competes with sodium, potassium, magnesium, and calcium, replacing them in intercellular and bone environments, and it also affects neurotransmission [5,7,9].

The greatest number of lithium toxicity is the consequence of long-lasting therapy [3]. Symptoms of toxicity develop slowly. There is, so called, prodromal stadium which lasts up to 7 days and can be manifested by vomiting, diarrhea, sleepiness, rough tremor and muscle spasms, lethargy, tinnitus, unclear speech, nystagmus, and in more severe cases polyuria and polydipsia. The occurrence of these symptoms is somewhat correlated with lithium concentration in serum [1] but every increase of lithium in serum above therapeutically defined values leads to toxic phenomenon. Symptoms associated with serum levels of 1.2–2.0 mmol are usual mild and seldom

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cause death or persistent neurological deficit while there are information that lithium level more than 1.5 mmol may be toxic [5].

Complete clinical manifestation of lithium toxicity is characterized by few syndromes and the most significant ones are expressed in the central nervous system, cardiovascular system and kidneys [7,10,11]. Since lithium does not bond to plasma proteins and considering its low molecular weight, hemodialysis leads to quick decrease of serum concentration giving false picture of rapid drug elimination. Unfortunately, due to fast redistribution, after hemodialysis, plasma values almost reach the level before dialysis and often require re-dialysis. It is also determined that the rebound-effect and sudden leaps of lithium concentration occur after hemodialysis [1,12,13]. Hemodialysis is the treatment of choice for rapid removal of lithium from the body, especially in cases of toxicity with higher lithium levels [14].

This case illustrates some of the factors that lead to lithium toxicity as well as the need to consider lithium toxicity to the differential diagnosis of a patient presenting with renal insufficiency with or without change in mental status and neurologic symptoms.

2. Case report

Male MN, 63 years old, has reported to Emergency department of the Clinical Center due to sleepiness, psychomotor slowness, exhaustion, oliguria.

At the admission, the patient was conscious, oriented, afebrile and obese, with slowed moves and less visible excoriations and burns on his face and lower limbs. Auscultation presented with diffusely atonic respiratory noise with prolonged exhalation. Cardiovascular examination revealed rhythmic heart action; tones were silent, with audible precordial systolic noise. Abdomen was palpatory insensitive. Blood pressure was 120/80 mmHg. ECG shows sinus rhythm (76-80 beats/min) without a change in final oscillation.

Radiographic exam of lungs and heart shows normal findings. Ultrasound exam of urinal tract and CT scan showed normal findings.

On the day of admission laboratory values of urea up to 23.2 mmol/L (normal: 3.0-8.0), creatinine 561 μmol/L (normal: 49-106), sodium 157 mmol/L (normal: 137-147), potassium 5.3 mmol/L (normal: 3.8-6.1) and blood glucose 4.7 mmol/L (normal: 3.8-6.1), pO2 7.6 kPa (10.7-13.3), pCO2 5.9 kPa (4.7-6.0), oxygen saturation 88 % (95-98%), pH 7.25 (7.35-7.45), base excess (BE) mmol/L - 13((-3)– (+3)), lactate 4.8 (0.5-2.2) mmol/L. Symptomatic therapy and intensive electrolytic status correction were started immediately after admission with iv saline and furosemide.

By continuous laboratory monitoring during the next 3 days, the values of laboratory analysis which show development of acute renal insufficiency (urea 30.7 mmol/L, creatinine 850 μmol/L, potassium 6.7 mmol/L, sodium 183 mmol/L). In the meantime, patient appeared to be confused and deep somnolent as well as facial and both wrist swellings which were followed by neurological extrapyramidal symptomatology.

After admission, we obtained some important data about medical history of this patient. We got data that he had sudden loss of conscience while burning down some hay on his countryside household, 2 days before admission– after which the listed difficulties have occurred. We also found out that he had a diabetes mellitus for 7 years and he was on oral antidiabetics (metformin 2000 mg per day). The patient was taking tablets of Lithium carbonate in dose of 900 mg per day for several years back. He did not control plasma level of lithium. Also, he was regularly taking tablets of Maprotiline in dose of 125 mg per day and tablets of Haloperidol in dose of 4 mg per day. No data about course of psychiatric illness because patient was treated in different psychiatric institutions. All medication mentioned was stopped after admission.

Simultaneously, due to the doubt of lithium toxicity, patient's blood was taken for determining lithium concentration. The patient's lithium level at the third day was 1.46 mmol/L (therapeutic blood level 0.4 to 1.2 mmol/L). We did not check lithium level as a routine analysis so we assumed that lithium level was higher at the time of admission.

Although there was electrolyte disbalance correction achieved to some level this patient was prepared for active depuration which was started instantly.

With everyday hemodialysis patient's state of mind improved and we achieved appropriate further fall of values of nitrogen substances in serum. The total of 10 hemodialysis in 10 consecutive days (each hemodialysis lasted 2 hours) was conducted in standard procedure for treating acute renal insufficiency. By following values of lithium concentration in blood, these levels were registered: after fifth hemodialysis 1.17 mmol/L and after 10th it was in range of reference values. Complete recovery of renal function with normal diuresis and artery tension values was verified in laboratory.

The patient was discharged from the hospital after 17 days with urea and creatinine values within normal range. Seven days after discharged, he was also in a good general state and still without psychiatric therapy introduced.

3. Discussion

Acute lithium toxicity most frequently occurs during its chronic use due to the overdose or too large dose of the drug given to the person with renal failure/disorder. Sometimes it happens in patients on Lithium with lack of sodium (fever, diet, diuretic use, dehydration).

Following factors are listed as significant in lithium intoxication/ toxicity: predisposition, drug interaction [15], nephrogenic diabetes insipidus, age above 50 years, thyroid dysfunction, creatinine clearance under usual values [16] and concomitant medication [15]. In patients treated with lithium, medical conditions that may lead to renal impairment and decrease the glomerular filtration rate also increase the risk of lithium toxicity. These conditions include aging, hypertension, diabetes mellitus, congestive heart failure, and chronic renal failure [14].

Described development of clinical manifestation of our patient went in favor of slow prodromal symptom occurrence characteristic for lithium toxicity. Severity of chronic lithium toxicity in this case was provoked by hemoconcentration arisen from dehydration (exposure to hot air and insolation for 4 hours). Although lithium concentration in our patient was not greater than 2 mmol/L (which is absolute indication for hemodialysis), we were guided by expressed clinical manifestation of this toxicity in two clinical syndromes: on central nervous system and kidneys.

The patient was also on combined psychiatric therapy with tricyclic antidepressant and neuroleptic along with lithium, which is also considered as one of additional factors [18]. Namely, it is known that antipsychotic haloperidol can increase toxicity of lithium [15] even with normal lithium values in serum, while on the other hand, lithium increases pharmacologic effects of tricyclic antidepressants [4].

One of reasons for acute renal insufficiency in this case was delayed lithium elimination. Hemoconcentration arisen from dehydration with sodium level of 157 mmol/L and 183 mmol/L contributed to lithium delayed elimination. At the admission, we did not have information about diabetes nephropathy in this case or some other renal preexisting condition but Diabetes mellitus is one of medical conditions that may lead to renal impairment and increase the risk of lithium toxicity also [14]. We did not start hemodialysis from the first day because intensive electrolytic status correction with iv saline and furosemide improved dieresis from 30 ml/hour to more than 50 ml/hour on the second day as well as there was no hyperkaliemia. Decision about hemodialysis was made on third day when we got lithium level as well as progressive increase in serum creatinine and blood urea level was registered.

Effectiveness of hemodialysis in therapy of serious acute lithium intoxication was confirmed in many studies [19-23]. However, toxic symptoms do not always correlate with plasma concentrations [24]. There is some correlation between Li serum levels and the severity of symptoms of intoxication [1]. There are various recommendations which refer to usage of hemodialysis in cases of various levels of drug in blood [13,25,26]. Certain number of authors does not recommend use of hemodialysis in cases when lithium concentration is above 4 mmol/L [27,28]. The decision to undertake a hemodialysis should be made some 8-12 h after admission and should be based on the patient's clinical condition, the serum lithium level and the spontaneous lithium kinetics [20,27-29].

Patient described in this case is a good example of possible difficulties in choosing the optimal treatment. Patient was on lithium therapy for several years; had no significantly increased level of lithium in serum, but was manifesting symptoms of toxicity (Naranjo Scale score 5 (5-8 = probable ADR) [30]. Severity in this case was provoked by hemoconcentration due to dehydration. Despite the fact that level of drug was 1.46 mmol/L, we decided for hemodailysis due to the clinical manifestation of poisoning expressed by two organs: kidneys and CNS. Diabetes mellitus is surely significant factor that contributed to acute renal insufficiency, as well as combination of lithium and tetracyclic antidepressant and antipsychotic.

4. Conclusion

The extensive differential diagnosis of a patient presenting with change in mental status and neurologic symptoms should include lithium toxicity. After lithium toxicity is confirmed, management depends on the lithium level as well as the clinical presentation. Hemodialysis is the treatment of choice for severe lithium intoxication but we still don't have sharp criteria when.

By respecting the principle that we should treat the patient, and not the level of lithemia, we contributed to the successful treatment, without sequelae.

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References

[1] Meltzer E., Steinlauf S., The Clinical Manifestations of Lithium Intoxication, IMAJ, 2002, 4, 265-267

[2] Cade JFJ., Lithium salts in the treatment of psychotic excitement, Med J 1949, 2, 349-352

[3] Dreisbach RH., True BL., Trovanja-prevencija, dijagnostika i lečenje, Data status Beograd, 2005, 525-527, (In Serbian)

[4] Nemeroff CB., Schatzberg AF., Recognition and treatment of psychiatric disorders - a psychopharmacology handbook for primary care, American psychiatric press Washington, London, 1999, 104-105

[5] Young W., Review of Lithium Effects on Brain and Blood, Cell Transplantation, 2009, 18, 951–975

[6] Varagić M., Farmakologija, 12th ed., Elit Medica Beograd, Beograd, 1996, (In Serbian)

[7] Joksović D., Akutna trovanja lekovima, 1st ed., Rivel Co Beograd, Beograd, 1999,(In Serbian)

[8] Thomsen K., Shirley DG., A hypothesis linking sodium and lithium reabsorption in the distal nephron, Nephrol Dial Transplant, 2006, 21, 869-880

[9] Nasiadek M., Chmielnicka J., The trace elements in response to lithium intoxication in renal failure, Ecotoxicology and Environmental Safety, 2003, 55, 178–183

[10] Kayrak M., Ari H., Duman C., Gul EE., Ak A., Atalay H., Lithium intoxication causing ST segment elevation and wandering atrial rhythms in an elderly patient, Cardiology Journal, 2010, 17, 4, 404–407

[11] Timmer RT., Sands JM., Lithium Intoxication, Journal of the American Society of Nephrology, 1999, 10, 666-674

[12] Reeves RR., Pendarvis BS., Kimble R., Unrecognized Medical Emergencies Admitted to Psychiatric Units., American Journal of Emergency Medicine, 2000, 18, 390-393

[13] Jaeger , Sauder JK. , Jaegle ML ., Toxicokinetics of Lithium Intoxication Treated by Hemodialysis., Clinical Toxicology, 1986, 23, 7-8, 501-517

[14] Delva NJ., Hawken ER., Preventing lithium intoxication, Can Fam Physician 2001, 47, 1595-1600

[15] Schou M., Lithium Prophylaxis: Myths and Realities, Focus, 2003, 1, 53-57

[16] Leblanc M., Raymond M., Bonnardeaux A., Isenring P., Pichette V., Geadah D., et al., Lithium poisoning treated by high-performance continuous arteriovenous and venovenous hemodiafiltration, American Journal Kidney Disease, 1996, 27, 3, 365-372

[17] Groleau G., Barish R., Tso E., Whye D., Browne B., Lithium Intoxication: Manifestations and Management, Aamerican Journal of Emergency Medicine, 1987, 6, 5

[18] Glendon CH., Lithium. In: Goldfrank LR., Flomenbaum NE., Weisman RS., Howland MA., Hoffman RS, (Eds.), Goldfrank's toxicologic emergiencies, 6th ed., Stamford, Connectitut: Appleton&Lange; 1998

[19] Hauger RL., O'Connor KA., Yudofsky S., Meltzer HL., Lithium toxicity: when is hemodialysis necessary?, Acta Psychiatrica Scandinavica, 1999, 81, 515-517

[20] Peces R., Pobes A., Effectiveness of haemodialysis with high-flux membranes in the extracorporeal therapy of life-threatening acute lithium intoxication, Nephrol Dial Transplant, 2001, 16, 1301-1303

[21] Beckmann U., Oakley PW., Dawson AH., Byth PL., Efficacy of continuous venovenous hemodialysis in the treatment of severe lithium toxicity, Journal Toxicology Clinical Toxicology, 2001, 39, 4, 393-397

[22] Peces R., Fernández EJ., Regidor D., Peces C., Sánchez R., Montero A., et al., Treatment of acute lithium intoxication with high-flux hemodialysis membranes, Nefrologia, 2006, 2, 3, 372-378

[23] Warning WS., Management of Lithium Toxicity, Toxicological Reviews, 2006, 4, 25, 221-230

[24] Balkhi S., Megarbane B., Poupon J., Baud FJ., Galliot-Guilley M., Lithium poisoning: Is determination of the red blood cell lithium concentration useful?, Clinical Toxicology, 2009, 47, 1, 8-13

[25] Baylisse G., Dialysis in the poisoned patient., Hemodialysis International, 2010, 14, 158-167

[26] Meertens JHJM., Jagernath DR., Eleveld DJ., Zijlstra JG., Franssen CFM., Haemodialysis followed by continuous veno-venous haemodiafiltration in lithium intoxication; a model and a case, European Journal of Internal Medicine, 2009, 20, 70-73

[27] Hansen HE., Amdisen A., Lithium Intoxication-Rreport of 23 cases and review of 100 cases from the literature, QJ medicine 1978, 47, 123-144

[28] Amdisen A., Clinical features and management of lithium poisoning, Medical Toxicology, 1988, 3, 18-32

[29] Benoit B., Michael M., Lithium Poisoning From a Poison Control Center Perspective, Therapeutic Drug Monitoring, 2000, 22,6, 650-655

[30] Naranjo CA., Busto U., Sellers EM et al., A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther., 1981, 30, 2, 239-245