

The 'SILENT Alarm': When History Taking Reveals a Potentially Fatal Toxicity

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ABSTRACT

Introduction: The combination of acute/sub-acute neurological and metabolic derangements should always raise the suspicion of toxicity, either endogenous or exogenous. The adverse effects of psychiatric medications are especially difficult to determine since the psychiatric background of patients is often inaccessible.

Clinical Presentation: A 66-year-old man presented to the emergency department with dysarthria and uncontrolled tremor, rapidly deteriorating into a complex of severe neurological and metabolic derangements. Only after repeated attempts to take a thorough history was lithium toxicity identified.

Conclusion: Thorough, comprehensive history taking, including chronic medications and their substitutes, is essential and lifesaving when potentially lethal medications are involved.

LEARNING POINTS

- Meticulous direct and collateral history taking is essential for correct diagnosis and to reveal psychiatric diagnoses and medications not reported by patients and caregivers.
- As drug interactions can cause potentially fatal side effects, it is of the utmost importance to gain access to the patient's full medication list.
- It is important to educate patients about the potential toxicity of their prescribed medications and to encourage them to seek medical attention when serious manifestations of toxicity are present.

KEYWORDS

Lithium, SILENT syndrome, history taking, bipolar disorder, drug toxicity

CASE PRESENTATION

One week before the index hospitalization, a 66-year-old male teacher visited the emergency department of another hospital. His main complaint was speech disturbances and uncontrollable tremor throughout his entire body. Medical history taking revealed chronic renal failure (baseline creatinine 1 mg/dl). He also had been taking medications for hypertension and dyslipidaemia. Physical examination revealed profound tremor, dysmetria and ataxia. Laboratory tests showed increased serum creatinine levels. A brain CT scan was normal. The patient

was discharged and recommended to undergo follow-up kidney function tests, urinary tract ultrasound, neurological examination and psychiatry follow-up.

A week later, the patient's condition deteriorated. He continued to have tremor and speech disturbances, and developed lack of appetite, insomnia, incomprehensible speech, ataxia, confusion, stuttering, agitation and disorientation. He therefore visited the emergency department of our hospital. His vital signs were normal and he was conscious but not communicating. Psychiatric evaluation noted he was restless and agitated. He was place-oriented but not time-oriented, with dysarthria and partial anomie. He denied delusions or perception disturbances, as well as any intention to self-harm.

Only then did his wife reveal that he had bipolar disorder and had been taking lithium for the previous 25 years, at a daily dose of 300 mg. He also had been recently prescribed an ACE inhibitor by a nephrologist who did not know about his psychiatric background. Following this new information, a very high lithium serum level (3.4 mmol/l) and cerebrospinal fluid level (1 mmol/l) were measured. An increased creatinine level (1.22 mg/dl) and hypernatraemia (157 mEq/l) were also detected. Due to his reduced level of consciousness, the patient was intubated and sedated, and later transferred to the ICU.

During ICU admission the patient developed generalized seizures with right gaze deviation. He was started on IV levetiracetam and midazolam. An EEG was normal. The patient opened his eyes upon attempted withdrawal of sedation. Extrapyrimal signs with a positive glabellar reflex were noted. The clinical course in the ICU included prolonged respiratory insufficiency and as there was no significant neurological improvement, the patient underwent tracheostomy. Nephrogenic diabetes insipidus was noted: his serum creatinine reached 1.7 md/dl with normal urinary output. As serum lithium levels were 1.8 mg/dl without clinical improvement, the patient was started on haemodialysis. Hydrochlorothiazide 12.5 mg twice daily was also initiated.

After several days the patient was transferred to the internal medicine department, where the following neurological findings were noted: a Glasgow coma scale of 4, profound tremor of the upper limbs and abnormal eye movements. Other elements of his physical examination were normal. *Table 1* gives the laboratory results.

During his stay in our department, treatment with amiloride was started, the patient received hydration and he improved clinically: he moved his limbs, tried to talk, asked for water and started to communicate. A month after admission, he was transferred to the rehabilitation department, there he began to walk and talk. He was discharged home after 2.5 months in hospital.

	Patient's values		Normal range
Urea (mg/dl)	69	↑	15-45
Creatinine (mg/dl)	1.52	↑	0.67-1.17
Sodium (mEq/l)	161	↑	136-148
Chloride (mEq/l)	125	↑	98-110
Potassium (mEq/l)	4.4	↔	3.5-5.2
Osmolality (calc.) (mOsm/kg H ₂ O)	341	↑	275-295
Protein (total) (g/dl)	6.2	↓	6.5-8.2
Albumin (g/dl)	2.6	↓	3.6-5.5

Table 1. Patient's serum blood tests upon arrival at the internal medicine department.

DISCUSSION

Considering all data, it is likely that an acute-on-chronic kidney injury (due to initiation of ACE inhibition) caused an abrupt increase in serum lithium levels. The literature indicates that renal clearance of lithium is reduced by approximately 25% by diuretics (and especially thiazides), thus necessitating lithium dosage reduction. ACE inhibitors, as well as other RAAS inhibitors, might also increase serum lithium concentrations and promote toxicity^[1].

Most cases of lithium intoxication do not arise from deliberate or accidental ingestion of increased doses of the drug. However, 'therapeutic overdoses' might occur due to accumulation of lithium in the circulation and tissues resulting from unrelated physiological changes such as hyponatraemia, use of diuretics, or varying renal function. Since the tissues will have already equilibrated with the blood^[2], high plasma lithium concentrations may not reflect the true degree of toxicity and so values above 2 mEq/l should be considered to indicate toxicity^[3].

Treatment for lithium-induced nephrogenic diabetes insipidus includes discontinuation of lithium and administration of amiloride^[1], which acts as a reversible inhibitor, competing with lithium on the binding site in the renal tubules, thus reducing lithium reabsorption.

Our patient had most of the risk factors for developing lithium toxicity and syndrome of irreversible lithium effectuated neurotoxicity (SILENT)^[1,4], which consists of prolonged neurological and neuropsychiatric symptoms. Neurological toxicity develops in tandem with elevated lithium concentration, and in typical cases persists despite successful removal of the drug (e.g. via haemodialysis). Patients may present with cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, dementia, nystagmus, choreoathetoid movements, myopathy and even blindness. SILENT may continue for months and in rare cases, years.

Risk factors for developing lithium-associated neurotoxicity and SILENT include age above 50 years, chronic lithium therapy, development of nephrogenic diabetes insipidus, hyperthyroidism and impaired renal function (e.g. with concurrent administration of NSAIDs and ACE inhibitors) as seen with our patient.

Most importantly, this case report highlights the importance of taking a complete patient and collateral history, including past medical psychiatric diagnoses and medications.

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