Persistent lithium-induced neurotoxicity: direct effect of lithium and/or hypernatremia?

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Case report

A 54-year-old African-American woman was brought to the emergency department of a university medical center with increased confusion. Over several days prior to presentation, she had become drowsy and disoriented. On the day of her admission she had her clothes on inside out. She did not have any nausea, vomiting or diarrhea, and there were no recent changes in her medications. She was previously diagnosed with bipolar disorder type I, and her medications were lithium carbonate extended-release 450 mg at nighttime, valproic acid 500 mg bid, fluphenazine 30 mg bid, and benztropine 2 mg bid. She had had prior episodes of lithium toxicity. The patient was followed in a community mental health center and, unfortunately, no information was available about how her previous episodes of lithium toxicity were characterized, and more importantly why the lithium was reinstated by her outpatient psychiatrist following these episodes. Physical examination showed a fine resting tremor. The patient was afebrile, with blood pressure of 124/73 mm Hg and pulse of 104 BPM. Initial serum electrolytes were unremarkable (including Na+ of 143 mmol/L), but the creatinine was 2.3 mg/dL. Creatine kinase, ammonia, TSH, folate, vitamin B12 were unremarkable, and WBC count was 12.7 (cells x 1000/microliter). Serum lithium level was 2.4 mEq/L, and valproic acid level was 48 mEq/L.

Computed tomography (CT) of the head revealed only mild cerebral atrophy. A psychosomatic medicine consultation was accomplished. On examination, the patient was

disheveled, alert, with poor eye contact, and disoriented to time and place. Speech was mildly dysarthric. She had bilateral mild tremor of the upper extremities. Psychiatric diagnoses were delirium, secondary to lithium intoxication, and bipolar disorder, type I. Lithium, fluphenazine, and benztropine were stopped, valproate was continued, and she was admitted to the internal medicine service.

During the next first 24 hours of hospitalization, the patient had increasing shortness of breath and became obtunded. A Foley catheter was placed and 3 liters of urine were obtained. Repeated physical examination indicated decreased level of consciousness with lack of response to painful stimuli, tachypnea, and tachycardia. Serum sodium was now increased to 168 mmol/L, creatinine was 2.3 mg/dL, urine osmolality was 147 mOsm/kg, urine Na+ was 42 mmol/L, and lithium level was 2.2 mEq/L. The new severe hypernatraemia was felt to be due to nephrogenic diabetes insipidus (NDI) secondary to lithium toxicity. The patient was transferred to medical intensive care unit (MICU).

In the MICU, a free water deficit (6 liters) was replaced over the next 36 hours, with normalization of her sodium. The free water deficit was replaced as 200cc free water per hour through her NG tube and 150 cc/HR plus urine losses through IV fluids with ½ normal saline. The sodium level was monitored every four hours and was corrected at a rate averaging less than or equal to 1 mmol/L per hour. The lithium level decreased steadily but slowly, as she still had a lithium level of 0.3 mEq/L on her 8th inpatient day. Repeated lithium levels showed 0.2 mEq/L on her 9th inpatient day, then 0.1 mEq/L in her 11th and 12th inpatient days. Lithium levels were monitored upon discharge, showing

a constant level of < 0.1 mEq/L. Her level of alertness slowly improved as her sodium normalized and her lithium finally cleared.

After her ICU stay, she was transferred back to the general medicine floor. Despite her having recovered a full level of consciousness, she was now nonverbal and also presented with new bilateral upper extremity wrist drop. Magnetic resonance imaging (MRI) of the brain, obtained on the 13th hospital day, showed small areas of flair hyperintensity in the left splenium and body of corpus callosum, with a tiny focus in the white matter of left temporal lobe, findings consistent with demyelination. An electroencephalogram (EEG) on the 14th hospital day showed diffuse slowing consistent with generalized encephalopathy, in addition to focal intermittent centrotemporal slowing, and no epileptiform discharges.

A neurological consultation (on the 15th hospital day) demonstrated diffuse hyperreflexia and clonus bilaterally in the lower extremities, bilateral wrist drop, mutism, and frontal release signs. The neurological consultant concluded that her altered neurological status was probably of a toxic/metabolic etiology, given her episode of lithium toxicity and hypernatraemia. An electromyography (EMG) study for the wrist drop indicated no lower motor neuron pathology. Subsequently, a MRI of the spine was ordered, which showed mild multilevel degenerative changes and no evidence of cord abnormality. A medical toxicology consult was called and could find no other toxicity to explain her persistent neuropsychiatric findings beyond the lithium toxicity.

During the next 20 days of hospital stay the patient started speaking, using short sentences. She showed gradual improvement in her amount of speech and cognitive function. On her 29th hospital day, the patient scored 14/25 (she was unable to attempt the three-step task, copy design, and sentence writing tasks due to persistent weakness of the upper extremities) on the MMSE, with the main impairments in attention, calculation, and recall sections. Throughout her hospitalization, her mood and affect remained well controlled on a therapeutic level of valproate, and she had no motor agitation suggesting a manic episode.

A nephrology consult (27th hospital day) reaffirmed the presence of chronic kidney disease, stage III, secondary to lithium toxicity, with tubulointerstitial nephritis. A second EEG done on her 27th hospital day was characterized by the presence of intermittent independent bilateral temporal polymorphic slowing. The neurologist commented that lithium, even at therapeutic levels, can cause pronounced EEG changes. As lithium had been stopped the day of her admission, these changes are still present after one month from its discontinuation.

Discussion

Our patient presented with acute neurological changes with an initial lithium level of 2.4 mEq/L. Cleveland described, for the first time, acute severe neurological disturbance resulting from lithium intoxication, in the absence of gastrointestinal symptoms (1). Our patient also presented with prolonged delirium after lithium was discontinued and hypernatraemia corrected. One week after admission, she presented with diffuse hyperreflexia, clonus, mutism, frontal lobe release signs, and bilateral wrist drop. The MRI of the brain showed changes suggestive of demyelination, while the EMG and MRI of the spine could not explain the wrist drop. The altered mental status was substantiated by the first EEG findings. The second abnormal EEG was consistent with the persistent functional brain changes, lagging well behind the discontinuation of lithium.

A similar case was reported by Lang and Davis, who described a 44 year old man with a two-month history of dysarthria, ataxia and leg weakness, at a serum lithium level of 1.5 mEq/L (2). On cessation of lithium, he partially recovered, the main persistent sequelae being cerebellar ataxia. Extensive investigation could find no cause other than chronic lithium toxicity to explain his cerebellar and pyramidal signs, despite serum lithium levels that had been monitored regularly. Another case report described a 60-year-old man who developed delirium after lithium administration at a serum level of 0.97 mEq/L, and showed persistent delirium for more than 1 month after discontinuation (3). Lithium-induced delirium generally improves within 1 week after discontinuation (4). It has been reported that abrupt discontinuation of lithium administration induced the development

and persistence of delirium in patients with serum lithium concentrations within or above the therapeutic range (5).

Lithium toxicity may be life threatening, or result in persistent cognitive and neurological impairment. Hemodialysis is used for severe lithium intoxication, very high serum levels, rising serum levels, or progressive clinical deterioration (6). Although hemodialysis is highly effective in removing circulating lithium, serum concentrations may rebound so repeated or prolonged treatment may be required (7).

Clinical manifestations of lithium toxicity effects may lag behind changes in serum lithium concentrations, due at least in part to delayed distribution into tissues (8). Therefore clinical recovery after lithium intoxication may take several weeks, with neurological symptoms persisting long after lithium levels have normalized. Also the levels of lithium in the blood may not accurately reflect brain lithium levels.

Most episodes of neurotoxicity are reversible on cessation or dose reduction and irreversible lithium toxicity is uncommon (9). Adityanjee described the concept of persisting neurological sequelae of lithium intoxication and named it the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) (10). In a recent review the same author identified 90 cases of SILENT in peer-reviewed publications, ranging from the typical signs of cerebellar dysfunction to atypical presentations like central pontine myelinosis and retrobulbar optic neuritis (9). The inclusion criteria were 1) causation of these neurological dysfunctions by lithium carbonate in the absence of prior neurological

illness and 2) the persistence of the sequelae for varying periods beyond two months after the cessation of lithium. Though we followed up this patient for only one month, we can argue that, given the severity of her sequelae, they might well persist beyond the two months criterion for SILENT. Also, the MRI findings suggestive of demyelination resonate with the proposed biologic mechanism of SILENT, which involves demyelination at multiple sites (10).

Our patient experienced hypernatremia, and rapid correction of serum sodium has been implicated as a potent causative factor for central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) (11). Those osmotic demyelination syndromes are rapidly progressing, often fatal focal symmetric syndromes, with clinical features ranging from a mild tremor or dysarthria to a progressive quadraparesis and a locked-in-syndrome. Our patient did not experience rapid correction of her sodium levels, and also there were no signal changes within the pons on the MRI of the brain, which make a diagnosis of CPM less probable. Also, as evidenced above, cases of SILENT, such as ours can include atypical presentations resembling CPM/EPM (10).

The concurrent psychotropic medications and their pharmacological forms might have played a role in her condition. Our patient was also taking fluphenazine and valproic acid and SILENT was reported in such a case (12). The absorption of slow-release preparations, as our patient's lithium prescription, has been found to be erratic, and can lead to very high lithium concentrations (13). Our patient’s gender might have played a

role too, as both lithium intoxication and neurological sequelae have been observed to be more frequent among women compared with men (14).

Our patient had had previous episodes of lithium toxicity. Chronic lithium poisoning is associated with greater toxicity than that due to acute poisoning in lithium-naive patients (15). In a recent review, the strongest predictors of severe toxicity in chronic lithium poisoning were age > 50 years, the presence of nephrogenic diabetes insipidis (NDI), hypothyroidism, and impaired renal function, three of which were present in this patient (16). Lithium treatment is the most common cause of drug-induced NDI, affecting about 10% of patients treated with the drug for 15 years or more (17). The risk of NDI correlates with the duration of lithium therapy and its course is unpredictable even after cessation of the medication. NDI is a relatively rare cause of hypernatraemia caused by urinary losses (18). Our patient may have had previously undiagnosed NDI and on this admission developed hypernatraemia, which contributed to her prolonged altered mental status.

In terms of describing and attributing this patient's unfortunately persistent neurologic deficits following her lithium toxicity episodes, there is a challenge of attributing her symptoms to various disturbances. These include the "direct" CNS effects of lithium (as described in the SILENT syndrome), the effects of the brief (36 hour) period of hypernatremia (presumably from lithium-associated NDI, and excessively rapid correction of the hypernatremia. As the hypernatremia was corrected in a cautious

fashion, the mechanism of excessively rapid restoration of normal serum sodium levels is unlikely.

Hypernatremia itself, usually due to other factors than lithium-associated NDI, has been associated with neurological deficits, including altered mental status, focal neurologic deficits, agitation, lethargy, neuromuscular hyperactivity, rigidity, hyperreflexia, asterixis, myoclonus, chorea, spasticity, tremor, ataxia, seizures, coma, and death (19-23). CNS symptoms of hypernatremia are more common with serum sodium levels greater than 169 mEq/L (21). Anatomically, engorged cerebral vasculature, subcortical and subarachnoid hemorrhages, and venous sinus thrombosis have been reported in hypernatremia (20, 22).

In our case, we believe the bulk of the clinical evidence suggests neurologic impairment due to the direct neurotoxic effects of lithium, although a contribution to her condition from the brief period of hypernatremia cannot be definitively ruled out. The possible contribution of hypernatremia to our case strongly reinforces the need to closely monitor and manage the serum sodium, not merely the creatinine and lithium levels, in lithium toxicity cases.

Conclusions

Psychosomatic medicine psychiatrists are advised to be alert to the possibility of persistent neuropsychiatric sequelae from lithium toxicity in patients presenting with altered mental status and lithium toxicity. The duration of the lithium toxicity episode and the renal complications of nephrogenic diabetes insipidis and hypernatremia may contribute to the genesis of these complications. EEG, neuroimaging, neurology consultation and toxicology consultation may be needed to fully elucidate these clinical phenomena.

References

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