Persistent cerebellar dysfunction following acute lithium toxicity: A report of two cases

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Introduction

Neurological disturbances caused by lithium fall on a continuum from simple side effects (e.g., benign tremor) to acute neurotoxicity manifested as coarse tremor, dysarthria, ataxia, seizures, encephalopathy and coma related to supratherapeutic lithium levels, usually reversible with drug discontinuation or dose reduction.[1]

Rarely, lithium is reported to cause irreversible, permanent neurological sequelae such as cerebellar impairment, dementia, parkinsonian syndromes, choreoathetosis, brain stem syndromes, and peripheral neuropathies.[1] Atypical presentations may include persistent papilledema, optic neuritis, isolated downbeat nystagmus, central pontine myelinosis, and myopathy.[1] Adityanjee suggested that these persistent sequelae may be called the Syndrome of Irreversible Lithium-Effectuated Neuro Toxicity (SILENT).[2] Persistent cerebellar dysfunction is the most commonly reported sequela as found in a review of the published cases of SILENT.[3] To qualify for a diagnosis of SILENT, lithium-induced neurological dysfunctions should occur in the absence of prior neurological illness and should persist beyond 2 months after the cessation of lithium,[3] although the syndrome remains imprecisely defined.

Here, we report two cases of persistent cerebellar syndrome following acute lithium toxicity and discuss them in the light of existing literature. Both the cases presented to Department of Psychiatry, Sheth V.S. General Hospital, Ahmedabad, India.

Case Reports

Case 1

A 35-year-old man diagnosed as having bipolar disorder had a history of two episodes of mania in 2004 and 2007. He was treated with lithium 1200 mg/day and olanzapine 20 mg/day (taken orally) on both the occasions, achieving remission in 3–4 months. Since then, he had always been on maintenance treatment of lithium 1200 mg/day. Just before the current admission, he experienced difficulty initiating sleep and had taken two extra tablets of lithium over and above the...
prescribed dose to induce sleep (total 2000 mg/day) for 2 consecutive days. He presented to the emergency room with bouts of vomiting, coarse hand tremors, and ataxic gait. He was restless but alert and oriented. He had dysarthria, finger-nose dysmetria, dysdiadochokinesia, and gaze-evoked nystagmus on examination. His brain magnetic resonance imaging (MRI), cerebrospinal fluid analysis and metabolic variables measured were normal. Abnormal laboratory investigations included serum lithium 4.42 mEq/l, creatinine 2.3 mg/dl, blood urea 68 g/dl, and thyroid-stimulating hormone (TSH) 10.52 μIU/ml. Repeat laboratory studies on the next day showed serum creatinine 4.6 mg/dl and blood urea 84 mg/dl. On examination, he had confusion, broad ataxic gait, and gross limb incoordination. He was then subjected to six sessions of hemodialysis. On day 12, his laboratory tests showed serum lithium 0.9 mEq/l, creatinine 1.2 mg/dl, blood urea 52 mg/dl, and TSH 4.51 μIU/ml. On discharge, he was still dysarthric, dysmetric on the finger-nose test, and unable to walk without support. He was only prescribed lorazepam 2 mg orally for sleep disturbance. At months 3 and 6 of follow-up, he had no manic or depressive symptoms but had an unsteady gait, saccadic dysmetria, disarticulate speech, static and intention tremors, and dysrhythmokinesia. All laboratory tests including renal and thyroid functions tested normal as did the repeat brain MRI. Serum lithium level was <0.2 mEq/l.

Case 2

A 55-year-old male had a 20-year history of bipolar disorder, with at least four manic episodes and several ill-defined depressive bouts. He had been on regular prophylactic treatment with lithium 900 mg and olanzapine 10 mg, taken orally as tablets. With a history of poor compliance to treatment for the last 1 year, he presented with severe manic features and was thus admitted. Lithium was restarted with 900 mg in two divided doses along with olanzapine 10 mg and clonazepam 2 mg (all medications were administered orally as tablets). All investigations including X-ray chest, electrocardiogram, and laboratory studies were normal. On day 3 of admission, he developed mild to moderate fever and cough with expectation. At that time, hemogram showed a total leukocyte count 14,100/cumm, but X-ray chest showed clear lung fields. He was diagnosed as having upper respiratory tract infection by the attending physician and was prescribed tablet cefadroxil 500 mg BD. Antipyretics were not administered. On day 5, he abruptly developed lethargy, disorientation, unsteadiness, nausea, abdominal pain, and diarrhea. Laboratory investigations showed total leucocyte count 15,200/cumm, serum lithium 2.52 mEq/l; hepatic, renal, thyroid, and other metabolic parameters tested normal. Brain MRI was normal. Lithium was discontinued and the patient was transferred to the medical intensive care unit. On day 10, he regained orientation while fever, cough, and other physical complaints subsided. However, while walking, he had a broad-based stance with truncal instability and a tendency to fall. In addition, there was finger-nose and knee-heel dysmetria with prominent intention tremors, as well as an evident rebound nystagmus. In the absence of any other neurological or psychiatric manifestations, he was discharged on olanzapine 10 mg and lorazepam 1 mg (taken orally as tablets); serum lithium being 0.3 mEq/l at that time. Even at 12 months of follow-up, he had a clumsy ataxic gait, with obvious limb incoordination and scanning dysarthria.

Discussion

Lithium overdose was clearly responsible for lithium toxicity in the first case, while in the second case, the exact reason for raised serum lithium level was not discernible. In the absence of lithium overdose or use of concomitant medications known to increase lithium level, the most plausible cause of lithium toxicity appears to be fever in the setting of infection. The concomitant medications used were olanzapine and clonazepam for mania and cefadroxil for upper respiratory tract infection. None of these three drugs is documented to escalate lithium levels. Antipyretics were deliberately avoided even in the presence of fever, as they are known to increase serum lithium level. Besides, he had been on lithium and olanzapine concomitantly for many (at least 5) years without any complications.

More often than not, long-lasting neurological sequelae are preceded by acute lithium poisoning,[2] as seen in both our cases. Possible risk factors predisposing to SILENT include high serum levels during acute intoxication, presence of fever, concomitant use of other drugs (e.g., antipsychotics, tricyclic antidepressants, and anticonvulsants), rapid correction of hyponatremia or lithemia, and coexistent illness, such as hypertension, renal failure, heart failure, acute gastroenteritis, and epilepsy.[14] Acute renal decompensation in our first case and fever in the setting of infection in our second case may be contributory factors in the genesis of the persistent syndrome.

Demyelination caused by lithium at multiple sites in the nervous system, including the cerebellum has been hypothesized to be responsible for the persistent deficits.[3] Neuropathologically, it is demonstrated that there is neuronal loss and gliosis in the cerebellar cortex and dentate nuclei with prominent spongy change in the cerebellar white matter.[3] There is especially a striking loss of cerebellar Purkinje cells caused by disrupted calcium homeostasis leading to plausible calcium-mediated neurotoxicity,[10] although the exact mechanisms are not well understood at this time.

We did report these two cases of lithium-induced cerebellar dysfunction to the adverse drug reaction (ADR) monitoring centre under PvPI at Smt. N.H.L. Municipal Medical College, Ahmedabad. The causality assessment was performed based on WHO criteria[7] and it was classified as a probable ADR to the drug looking into the reasonable time sequence of occurrence of the adverse event. event corresponded to what is known for the drug and event was not reasonably explained by patients’ disorder or other drugs. The reaction is termed as serious since it has led to persistent disability till the time of the last follow-up, long since lithium had been discontinued (the worldwide vigiflow number is as follows-report ID for case 1 is 2015-06069 and for case 2 is 2015-06070).

Conclusion

Clinicians need to be aware of the possibility of persistent neurologic sequelae that may follow acute lithium toxicity. A
precise definition and operational diagnostic criteria may help in the early identification and prevention of the syndrome.\textsuperscript{3}

\textbf{Financial Support and Sponsorship}

Nil.

\textbf{Conflicts of Interest}

There are no conflicts of interest.

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