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A Diagnostic Pitfall: Lithium Toxicity Mimicking Creutzfeldt-Jakob Disease

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Abstract

Lithium-associated neurotoxicity can rarely present as a Creutzfeldt-Jakob disease (CJD)-like syndrome, creating significant diagnostic uncertainty, particularly in older adults with multiple comorbidities. We describe the case of an 86-year-old woman with bipolar disorder on long-term lithium therapy, hypothyroidism, and hypertension, who developed progressive cognitive and functional decline over several years, followed by acute deterioration after elective surgery.

Serum lithium levels remained normal or at the upper limit of the therapeutic range; lithium neurotoxicity was suspected. EEG raised a concern for sporadic CJD; however, brain MRI showed no supportive features.

This case highlights the diagnostic challenge, where clinical and electroencephalographic findings closely mimic CJD. Neurotoxicity may occur even at therapeutic lithium concentrations, limiting the reliability of serum levels. Contributing factors such as age, comorbidities, polypharmacy, and acute illness may increase vulnerability. Early recognition and prompt withdrawal of lithium are essential, as this condition may be reversible, although outcomes may be poor in frail patients.

Categories: Neurology, Geriatrics, Internal Medicine
Keywords: bipolar disorders, creutzfeld-jacob disease (cjd), dementia etiology, lithium intoxication, periodic sharp wave complexes

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare and rapidly progressive neurodegenerative condition caused by abnormal prion proteins. It is the most common form of human prion disease and typically presents with a swift decline in cognitive function, often accompanied by myoclonus and other neurological features such as staggered gait and impaired fine motor control, Rigidity, bradykinesia, tremor, and pyramidal signs, for example, hyperreflexia, spasticity, and pathologic reflexes. The disease course is usually aggressive, with most patients deteriorating over months [1].

Lithium toxicity is a recognised complication of long-term lithium therapy, particularly in older patients and those with multiple comorbidities. Its neurological effects can vary widely, ranging from mild tremor and confusion to severe encephalopathy. Importantly, toxicity can occur even when serum lithium levels are within or close to the therapeutic range, especially in the context of intercurrent illness or polypharmacy [2].

The aim of this article is to highlight the diagnostic challenge of lithium-induced neurotoxicity mimicking CJD and to emphasise that significant neurotoxicity can occur despite therapeutic serum lithium concentration.

Lithium-induced CJD-like encephalopathy remains an uncommon but well-recognised mimic of prion disease, described almost entirely through individual reports and reviews since it was first characterised in patients who recovered fully after lithium withdrawal [3]. Reported cases have occurred predominantly in elderly patients [4], in whom neurotoxicity may arise at far lower serum levels than in younger patients [5] and for whom prophylactic targets of 0.4-0.6 mmol/l are advised [6]. Because serum levels within the therapeutic range do not exclude the diagnosis, and because recognition can avert costly, invasive and unnecessary investigative procedures in a condition whose prognosis contrasts sharply with that of true CJD [7,8], this case is documented to add a very elderly, multimorbid example in which the diagnosis rested on clinical reasoning alone and in which recovery was not achieved.

Case Presentation

An 86-year-old retired nurse with a history of bipolar disorder, hypothyroidism, hypertension, and a longstanding upper limb tremor experienced progressive mobility and cognitive decline over several years. The tremor, present for over a decade, became bilateral and coarse at rest and on action and significantly impacted her daily activities. Her mobility worsened due to a stooped posture, gait slowing, and recurrent

falls, accompanied by subtle cognitive changes noted by her family.

She was admitted and underwent bunion surgery in January 2023, which was complicated by postoperative delirium, pneumonia, and new atrial fibrillation, requiring intensive therapy unit (ITU) admission for three to four days. Slurred speech was noted shortly before the ITU transfer. Following ITU, she developed stiffness with extensor posturing of both lower limbs (described as “pointed like a ballerina”) and has been bedbound since.

During her prolonged hospitalization, she exhibited fluctuating cognitive function, slurred speech, visual hallucinations, and progressive limb stiffness. A *Clostridium difficile* infection required treatment, and lithium was temporarily withheld due to concerns over toxicity. Neurological findings included progressive flexor posturing of the upper limbs with contractures and generalized limb pain. She was alert but disoriented to time, place, and events and presented with high-pitched, whimpering speech and absent reflexes and plantar responses, along with a coarse upper limb tremor.

Investigations revealed diffuse slowing on EEG, triphasic waves, and periodic sharp wave complexes, raising concern for sporadic CJD, although these findings are not very specific for it (Figure *1*). However, MRI showed no convincing evidence of CJD, such as cortical ribboning, pulvinar sign, or basal ganglia hyperintensity, nor any acute abnormality (Figures *2A*-*2C*).

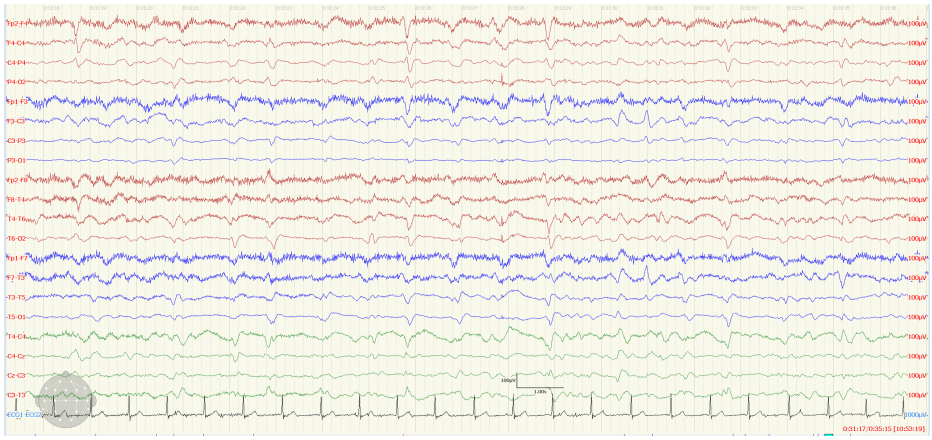


FIGURE 1: EEG showed triphasic waves, and periodic sharp wave complexes.

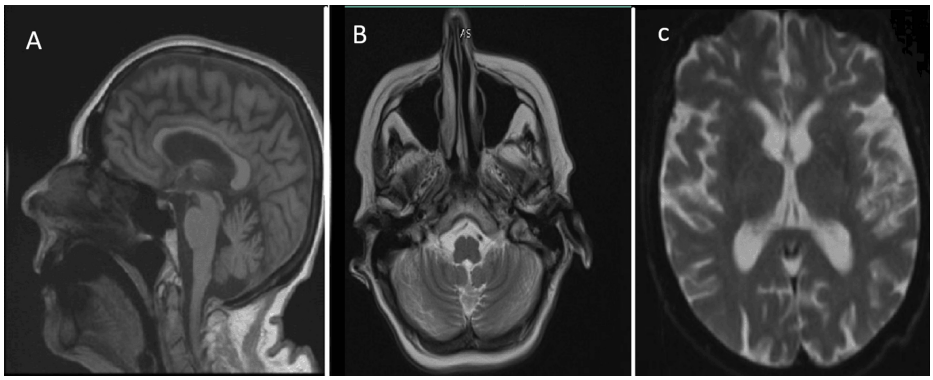


FIGURE 2: The MRI of the brain showed no convincing evidence of Creutzfeldt-Jakob disease.

Rapid cognitive decline with periodic discharges on EEG made sporadic CJD a serious early consideration. Against it, MRI lacked the characteristic cortical, pulvinar, or basal ganglia changes; the course fluctuated with partial recovery, and reflexes were absent rather than brisk. Her decade-long tremor, stooped posture, gait slowing, falls, fluctuating cognition, and visual hallucinations pointed instead to an underlying neurodegenerative disorder, probably Lewy body disease, with superimposed delirium after surgery and sepsis. The Neurology and CJD Team therefore considered neurodegenerative conditions more likely than CJD; CSF analysis (real-time quaking-induced conversion (RT-QuIC), 14-3-3), which could have excluded CJD

definitively, was recommended but declined by the family.

Although neurophysiology highlighted potential lithium toxicity mimicking CJD findings, lithium levels remained mostly within the therapeutic range (0.4-1.0). Lithium was temporarily withheld for two weeks, resulting in some improvement in appetite and cognitive function, then reintroduced on old age psychiatry advice at a reduced dose along with sertraline 50 mg, but a high lithium level was noted 10 days after restart (Table *1*). This suggests lithium neurotoxicity may have contributed despite therapeutic serum levels, which can underestimate brain concentrations, and shows her narrow margin of safety.

Collection date (of admission)	Level	Lower limit	Higher limit
Day 147 (Ten days after restarting)	1.2	0.4	1.0
Day 137 (After holding for two weeks)	<0.1	0.4	1.0
Day 116 AM	0.5	0.4	1.0
Day 116 PM	0.6	0.4	1.0
Day 112	0.8	0.4	1.0
Day 105	0.7	0.4	1.0
Day 98	0.6	0.4	1.0
Day 91	0.7	0.4	1.0
Day 83	0.5	0.4	1.0
Day 76	0.5	0.4	1.0
Day 61	0.5	0.4	1.0
Day 54	0.6	0.4	1.0
Day 47	0.8	0.4	1.0
Day 42	0.7	0.4	1.0
Day 34	0.5	0.4	1.0
Day 28	0.5	0.4	1.0
Day 24	0.4	0.4	1.0
Day 23	0.4	0.4	1.0
Day 19	0.5	0.4	1.0
Day 18	0.7	0.4	1.0
Day 17	1.0	0.4	1.0
Day 5	0.4	0.4	1.0
Day 3	0.2	0.4	1.0

TABLE 1: Lithium levels (all samples were taken between 9-10 AM)

She was later discharged to a nursing home following multi-disciplinary team and family agreement, as the family was keen for her to spend more time with them and for her to enjoy the rest of her life away from the hospital, with agreement to complete some investigations as an outpatient. Planned follow-ups included a CT of the thorax-abdomen-pelvis to rule out underlying malignancy, a repeat EEG in three months, and an autoimmune encephalitis panel, which was negative. Regrettably, she passed away one week post discharge.

Discussion

Across multiple case reports and reviews, lithium has been implicated in a reversible CJD-like encephalopathic syndrome, often presenting as a rapidly progressive dementia with characteristic EEG abnormalities. First described in English in a case review of two patients, Smith and Kocen developed subacute cognitive decline, confusion, speech disturbance, extrapyramidal features, tremor, rigidity, and

myoclonus, closely mimicking sporadic CJD. They highlighted, as did subsequent reports, that EEG showed a loss of normal rhythms with widespread slow activity and periodic sharp wave complexes, a pattern classically associated with CJD but also observed in lithium-related encephalopathy and other metabolic or iatrogenic encephalopathies [3]. A further four cases with similar presentations were reported in 1989 following the Smith and Kocen study: two by Primavera et al. [9], one by Kemperman and Notermans [10], and one by Broussolle et al. [11], which was associated with combined lithium and levodopa treatment.

Importantly, the effects of lithium in these cases were not reliably predicted by serum lithium concentrations. At least two reports have described patients who developed profound neurological syndromes while lithium levels remained within or only marginally above the therapeutic range, suggesting a dissociation between serum levels and neurotoxic effects [9,10]. EEG abnormalities in patients receiving non-toxic lithium levels are well documented, as in Casanova et al. [4], reinforcing the concept that lithium neurotoxicity may occur without overt biochemical evidence [12]. In the cases reviewed, lithium was the implicated medication; however, this was often prescribed alongside other medications, such as levodopa, sedating antihistamines, trazodone, benzodiazepines, etc. The recognition of myoclonus, hyperreflexia, tremor, and incoordination as features of serotonin syndrome is noted by Fear, who speculated that these features might be caused by the serotonin agonist effects of lithium. It is of note that in our case lithium was co-prescribed with sertraline [13].

The clinical consequences of lithium-induced CJD-like syndromes were frequently reversible, provided lithium was recognised as the causative agent and promptly withdrawn. Several cases demonstrated normalisation of EEG findings and substantial neurological recovery following lithium cessation, distinguishing this entity from true prion disease. However, delayed recognition was common, attributed to three key factors by Finelli: clinical features of progressive dementia/absence of signs of delirium, reliance on normal lithium levels, and limited awareness that lithium could mimic CJD [14]. While most reported cases avoided permanent neurological sequelae, the syndrome posed significant diagnostic and prognostic challenges and, in vulnerable populations, contributed to severe morbidity [9].

Our patient shared several core features with previously reported cases. She had subacute cognitive decline with speech disturbance, tremor and rigidity, and an EEG showing diffuse slowing, triphasic waves and periodic sharp wave complexes, closely resembling the picture that led Smith and Kocen to suspect sporadic CJD [3]. As in the reports of Primavera et al. [9], Kemperman and Notermans [10], Brown and Rosen [7] and Cameira et al. [8], clinical neurotoxicity was evident while serum lithium remained mostly within the therapeutic range.

Our case also differed from the published literature in several respects. First, earlier cases generally recovered substantially after withdrawal [3,11,14], whereas our patient improved only partially and remained bedbound. This is likely explained by her age (86 years) and a probable underlying neurodegenerative disorder, which reduce cerebral reserve and would make lithium one contributor among several rather than the sole cause. Postoperative delirium, pneumonia, ITU admission and *Clostridium difficile* infection added further insults, and the delay before lithium was withheld, a recognised problem in this syndrome [14], may have contributed to incomplete recovery. Second, earlier reports emphasised myoclonus and hyperreflexia [13], while our patient had absent reflexes with flexor and extensor posturing and contractures; myoclonus was not documented. This may reflect a later stage of illness, prolonged immobility, or an overlapping neurodegenerative process rather than a different toxic mechanism. Third, although her levels were mostly therapeutic, a high level was recorded 10 days after reintroduction at a reduced dose, which suggests reduced lithium clearance during intercurrent illness. This is consistent with marginally raised levels in earlier cases [9,10] and reinforces that a single “normal” level may not reflect brain exposure or risk. Finally, the normal MRI in our patient supports the exclusion of prion disease on imaging, whereas many early reports predate routine MRI. Because CSF RT-QuIC was declined and brain or erythrocyte lithium was not measured, attribution to lithium remains probable rather than proven.

Collectively, the literature underscores a critical learning point: any patient presenting with rapidly progressive dementia should undergo a meticulous drug history review, with particular attention to lithium exposure. Furthermore, therapeutic lithium levels should not rule out consideration of lithium as a cause of such deterioration and, if suspected, should be promptly stopped. More widely, given the adverse effects observed within therapeutic ranges, lithium doses should be maintained at the lowest effective level, especially in older adults, to mitigate against the risk of lithium-induced CJD-like encephalopathic syndrome [15].

Conclusions

This case highlights lithium-induced neurotoxicity as an important and potentially reversible mimic of CJD, particularly in older adults with multiple comorbidities. It underscores that significant neurological deterioration, including rapidly progressive cognitive decline, extrapyramidal features, and characteristic EEG abnormalities, can occur even when serum lithium levels are within or near the therapeutic range. Contributing factors such as advanced age, intercurrent illness, and polypharmacy may increase susceptibility to toxicity. Clinicians should maintain a high index of suspicion and prioritise a detailed medication review in such presentations. Early recognition and prompt withdrawal of lithium are essential to

optimise outcomes, although prognosis may remain poor in frail patients.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mahmoud Gaballah, Hiba Al-Bayati, Joseph Waters-Clark, Muhammad Ahmad

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Supervision: Mahmoud Gaballah, Hiba Al-Bayati, Joseph Waters-Clark, Muhammad Ahmad

Disclosures

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