The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity

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Objectives: Persistent sequelae of lithium intoxication gained clinical attention in the 1980s and were named Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT). The authors review the published cases of SILENT reported in the literature and discuss various clinical manifestations.

Methods: The authors' inclusion criteria included persistence of sequelae for at least 2 months after the cessation of lithium administration. They conducted a MEDLINE and Pub Med search for journal articles from the year 1965 to 2004. They also cross-referenced available papers.

Results: The authors identified 90 cases of SILENT in peer-reviewed publications. Persistent cerebellar dysfunction was the most commonly reported sequela. Other atypical presentations have also been reported.

Conclusion: Although the biologic mechanism remains unclear, the authors hypothesize that the putative cause of SILENT is demyelination caused by lithium at multiple sites in the nervous system, including the cerebellum. Recent advances in the understanding of the molecular basis of lithium-induced neurotoxicity may be able to provide a means of defining a pathway associated with the long-term prophylactic properties of lithium, distinct from its toxicity profile. This identification of differential gene expression patterns that distinguish between therapeutic and toxic actions of lithium may help in the discovery of new drugs for mood stabilization. Clinically and heuristically, it is important to raise the awareness of this syndrome so that clinicians are able to avoid it. A precise definition, operational diagnostic criteria, and a descriptive name will aid in the early identification and prevention of SILENT.

Key Words: neurotoxicity, lithium, cerebellar dysfunction

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Long before lithium was used in psychiatry, in a unique experiment conducted on himself, Cleveland,[1] in 1913, described for the first time the acute severe neurologic disturbance resulting from lithium ion intoxication, emphasizing the occurrence of it in the entire absence of gastrointestinal symptoms. The year of lithium's introduction to psychiatry (1949) also witnessed a series of reports on its neurotoxicity and occasional lethality.[2–5] One of these reports highlighted the potential of chronic toxicity developing insidiously in patients taking small doses of lithium over a long period of time.[3] Cade,[6] who introduced lithium to psychiatry, also talked about the acute neurotoxicity of lithium. Subsequently, a number of articles appeared on the acute neurotoxicity of lithium.[7,8] The possibility of persisting neurologic sequelae, however, was not given much attention. It was stated that patients with severe lithium toxicity either died or recovered completely,[9] despite evidence to the contrary.[10] In the 1970s, several cases were reported in which severe neurotoxicity occurred with "therapeutic" lithium levels.[11–24] Similar cases continued to be reported in the 1990s as well.[25,26] This seemingly puzzling occurrence was explained on the basis of tissue retention of lithium in the nerve cells.[14,27] Persistent neurotoxicity induced by a lithium–neuroleptic interaction was also reported,[28–31] as was persistent neuropsychological impairment with lithium.[32,33]

The earlier reports on irreversible neurotoxicity of lithium did not arouse much scientific curiosity.[12,19,34,35] The report by Cohen and Cohen[36] on irreversible brain damage caused by a combination of lithium and haloperidol generated considerable controversy and criticism.[19,21,37] It also led to the focusing of attention on the issue of irreversible neurotoxicity. Thereafter, a stream of case reports appeared,[15,38–51] but only a few authors dealt with this issue in a well-organized manner.[17,52–54] In an in-depth discussion on lithium neurotoxicity, Johnson[17] concludes that the emergence of neurotoxicity does not correlate with serum lithium levels, and the threshold of sensitivity to effects shows wide individual variations. Similar cases were seen with toxicity at therapeutic levels.[25,26]

Hansen and Amdisen[53] reviewed 23 cases of lithium toxicity that they personally encountered, in addition to 100 cases of lithium toxicity from published literature. They pointed out that, along with other factors, the duration of exposure to elevated serum lithium levels is also important in determining the outcome.[53] The neurologic sequelae generally develop following the abatement of acute intoxication and typically involve cerebellar dysfunction, although there are signs of damage at multiple sites in the nervous system.[52,54]

A few of the patients became clearly demented and others showed extrapyramidal features. However, Ghadirian and Lehman[55] are silent on this cumulative evidence in favor of persistent neurologic sequelae, maintaining that remission is the most likely outcome following cessation of lithium. Forty cases were included in a review in 1984 by Schou,[54] who also laid down the criteria for persistent neurotoxicity. Subsequently, a total of 48 cases were reported in an early 1987 review[56] (Table 1[57–59]). In the absence of any universally acceptable alternative, Adityanjee, in 1987, proposed a new descriptive acronym: SILENT—the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity.[57,60–62] This was first mentioned in a letter published in 1987.[57] This acronym descriptively explains the concept of persisting neurologic sequelae of lithium carbonate intoxication, and may help raise the awareness among clinicians about this important iatrogenic and irreversible syndrome, as lithium still remains a first-line mood stabilizer.

METHODS

We reviewed the long-term sequelae of lithium intoxication (SILENT) in depth to highlight their clinical presentation, assessment, management, and the need to take preventive steps to minimize their occurrence. We conducted a MEDLINE and Pub Med search for journal articles from the year 1965 to 2004 that dealt with cases that fit the description of SILENT. We also cross-referenced the available papers to identify sporadically reported cases. Our inclusion criteria were the same as Schou's,[54] and included the persistence of sequelae for at least 2 months after the cessation of lithium. We only included those cases that met the criteria laid down by Schou.[54] So, for example, in a case reported by Omata et al,[26] delirium disappeared 6 weeks after cessation of lithium, and this report consequently was excluded from our review because our criteria specify the persistence of sequelae for at least 2 months after the cessation of lithium.

RESULTS AND DISCUSSION

We identified a total of 90 cases of SILENT in the published literature (Table 2[63–99]). There were 49 female patients (58.3%) and 35 male patients (41.66%) ranging in age from 21 to 77 years (mean, 46.63 years; standard deviation, 13.74 years; n = 84). The doses at which the toxicity occurred varied from 438 to 8100 mg/day (not taking into account 1 case of attempted suicide [this person ingested 24,000 mg lithium carbonate and developed SILENT]; mean dose, 1403.68 mg/day; standard deviation, 1006.74 mg/day; n = 62). The reported serum levels ranged from 0.1 to 8 mM/L (mean, 2.29 mM/L; standard deviation, 1.67 mM/L; n = 79). Although there was a total of 90 cases identified by us, not all of them reported all the specifics, like age, gender, dose, serum level, and so forth. Hence, the mean and standard deviations for each of these parameters is based on different numbers of observations.

TABLE 1. SILENT Cases Identified

Author	n
Donaldson and Cunningham,[52] 1983	17
Schou,[54] 1984	40
Adityanjee,[56] 1987	48
Adityanjee,[57] 1987	55
Verdoux and Bourgois,[58] 1991	31
Kores and Lader,[59] 1997	50
Adityanjee et al, 2004 (this article)	90

Risk Factors

Age

Donaldson and Cunningham's[52] review of cases with persisting neurologic sequelae reported ages ranging from 34 to 65 years (mean, 53.6 years). Schou[54] mentioned an age range of 28 to 67 years (mean, 48 years), a little lower than the mean age of 52 years found in the selected cases of lithium intoxication in another series.[53] Age alone, however, gives no clue as to why permanent injury was sustained.[52] From the cases we reviewed from the literature (Table 2) that also reported age (n = 84), patient age ranged from 21 to 77 years (mean, 46.63 ±13.74 years).

Gender

Both lithium intoxication and neurologic sequelae after lithium intoxication have been observed to be more frequent among women compared with men.[54] However, rather than being due to a heightened susceptibility to lithium in women, this may merely reflect a prescribing bias on account of the greater proportion of women treated with lithium.[52] From the cases we reviewed from the literature (Table 2) that also reported gender (n = 84), there were 49 female patients (58.3%) and 35 male patients (41.66%).

Dose and Serum Levels

SILENT occurs even at therapeutic doses of the drug. From our review of cases (Table 2), the doses responsible for SILENT ranged from as low as 438 mg/day to as high as 8100 mg/day. This does not include a case of attempted suicide reported by Tesio et al,[84] where the patient ingested 24,000 mg lithium carbonate. (Because the dose in this case represents an outlier, we did not include it in the calculation of the mean and standard deviation.) The mean dose for the 62 cases that reported doses was 1403.68 ± 1006.74 mg/day. Also, from the cases we reviewed from the literature that also reported serum levels (n = 79), the patients' serum levels of the drug ranged from 0.1 to 8 mM/L (mean, 2.29 ± 1.67 mM/L).

Drug Combinations

Long-lasting sequelae with lithium alone have been described.[12,17,26,34,35,38,39,41,50,53,59,95,99] Long-lasting lithium neurotoxicity has also been described in combination with other drugs: haloperidol,[28,29,31,36,46,48,52,59,68,69,74,80,82,83,86] thioridazine,[47,70,85] phenytoin,[15,20,34] chlorpromazine[35,47,67,70,76,78,82,84,86] and mazindol.[100] In addition to lithium–neuroleptic combinations, SILENT has been reported in patients taking the following drugs in combination with lithium: amitryptiline,[25,42] aspirin,[25] verapamil,[25,69] valproate,[31] and erythromycin[59];

TABLE 2. Case Reports of SILENT in Published Literature (2004)

Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Verbov et al,[10] 1965; Favarel–Garrigues et al,[63] 1972	F/34	Nystagmus, instability in gait and standing	Infection	3000		Coma vigil, myoclonic seizure, general hypertonia, semimydriasis	
Von Hartitzsch et al,[35] 1972	F/50	Flapping hand tremor, ataxia, involuntary extrapyramidal type, nystagmus, choreoathetosis	Toxic plasma level	1600	5.00	Lethargy, ataxia, seizures, stupor, hyperreflexia, bilateral extensor plantar response, coma	Chlorpromazine
Von Hartizsch et al,[35] 1972	F/53	Ataxia, choreoform movements, tremor, choreoathetosis, bilateral extensor plantar response	Toxic plasma level	1600	2.30	Disorientation, ataxia, coarse tremor, seizures, stupor, hyperreflexia, bilateral extensor plantar response	
Juul–Jensen and Schou,[34] 1973	F/38	Dysarthria, nystagmus, ataxia, bilateral dysdiadochokinesis	Suicide and/or combination with phenytoin		5.60	Bilateral nystagmus, spasticity, hyperreflexia, myoclonus, grand mal seizures	Phenytoin
Juul–Jensen and Schou,[34] 1973	F/55	Ataxia, bilateral nystagmus	Gynecologic operation with dehydration	900	2.90	Tremor, rigidity, impaired consciousness	Phenytoin
Cohen and Cohen,[36] 1974	F/34	Dementia, mask face, involuntary movements, hypotonic muscles, CE, DE, EPS	Neuroleptic–lithium combination	1800	1.81	Fever, confusion, tremor, cogwheel rigidity, sialorrhea, stupor, involuntary movements, dysarthria, dysmetria ataxia, vertical nystagmus	Haloperidol, benztropine mesylate
Cohen and Cohen,[36] 1974	F/40	Dementia, mask face, tremor, hyperreflexia, hypotonia, dysarthria, ataxia, dysdiadochokinesis, dysmetria, CE, MED, EPS	Neuroleptic–lithium combination	1500	1.48	Fever, somnolence, tremor, muscular rigidity, ataxia, vertical nystagmus, dysarthria	Haloperidol, benztropine mesylate
Cohen and Cohen,[36] 1974	F/63	Choreoathetosis, resting tremor, cogwheel movements, buccofacial dyskinesia, CE, CA, EPS	Neuroleptic–lithium combination	1165	1.58	Fever, impaired consciousness, tremor, cogwheel rigidity, ataxia	Haloperidol
Cohen and Cohen,[36] 1974	F/63	Choreoathetosis, parkinsonian tremor, buccofacial dyskinesia, CE, EPS	Neuroleptic–lithium combination	1800	2.45	Fever, tremor, dysarthria, mask face, postural tremor, lead pipe rigidity, lethargy	Haloperidol
Goldwater and Pollack,[15] 1976	F/57	Slurred speech, spastic gait, impaired short-term memory and reasoning		438	4.8	Tremor, maskface, confusion, mouthing movements, vomiting, clasp knife spasticity, cogwheel rigidity, hyperactive reflexes, extensor plantars, oculogyric crises, opisthotonic attacks	Phenytoin
Johnson,[17] 1976	F/50	Ataxia, hyperreflexia, cerebellar incoordination, upward gaze palsy, CE, BULB, MED			3.00	Ataxia, slurred speech, fluctuating consciousness	
Hansen, and Amdisen,[53] 1978	M/65	Dementia		32 (mM)	2.1	Stupor	
Hansen and Amdisen,[53] 1978	F/45	Death		56 (mM)	4.8	Stupor	
Hansen and Amdisen,[53] 1978	F/63	Dementia		24 (mM)	3.2	Stupor	

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TABLE 2. *(continued)* Case Reports of SILENT in Published Literature (2004)

Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Speirs and Hirsch,[20] 1978	M/26	Tremor	Epilepsy and/or phenytoin	2400	0.80	Coarse tremor, hypertonia, hyperreflexia, coma	Phenobarbitone, phenytoin
Lobo et al,[41] 1978	F/29	Fundoscopic abnormalities		1800	1.2	Blurred vision, papilledema, nonspecific difficulties with eyes	
Julien et al,[64] 1979	F/62	Cerebellar signs		1000	2.69		
Newman and Saunders,[43] 1979	M/47	Ataxia, paraplegia			2.3	Ataxia, spastic paraplegia, mental deterioration, stupor	
Newman and Saunders,[43] 1979	F/42	Axonal neuropathy			1.9	Coma, flaccid paralysis, absent tendon reflexes, proximal muscle weakness	
Thomas,[48] 1979	F/58	Severe organic brain damage, considerable disorientation, impairment of memory			1.9	Extrapyramidal symptoms, rigidity, orofacial dyskinesia, confustional state, total disorientation	Haloperidol
Warick,[65] 1979	M/36	Cerebellar signs		2700	7.6		Sulphamethoxazole, chlorazepate
Pringuey et al,[45] 1981	M/54	Cerebellar signs		1500	3.8		Digitalis
Heim et al,[66] 1981	F/48	Cerebellar signs		1000	3	Neuropathy, choreoathetosis	Digitalis, anticoagulants, diuretics, carbimazole
Uchigata et al,[67] 1981	M/56	Dysarthria, ataxia, vertical nystagmus, peripheral neuropathy, CE, PN		1800	1.40	Fever, drowsiness, dysarthria, tremor, rigidity, ataxia, myoclonus	Chlorpromazine, levomepromazine
Spring and Frankel,[68] 1981	M/53	Dysarthria, turncal dyskinesia, CE, EPS	Diphenylhydrazine	2400	1.50	Fever, rigidity, stupor, cogwheeling, parkinsonian galt	Haloperidol (benztropine occasionally)
Baker et al,[69] 1981	M/37	Gait ataxia, dysarthria		2400	1.2	Delirium, fever, dysarthria, nystagmus, Legionnaire disease	Haloperidol
Sellers et al,[47] 1982	F/43	Ataxia, dysarthria,CE	Neuroleptic–lithium combination	750	1.20–2.50	Unconsciousness, rigidity, tremor, opisthotonus, ataxia, dysarthria, nystagmus	Chlorpromazine, thioridazine
Singh,[70] 1982	F/36	Dysarthria, CE	Neuroleptic–lithium combination	1200	0.25	Confustion, ataxia, dysarthria, coarse tremor	Chlorpromazine, thioridazine
Pamphlett and Mackenzie,[44] 1982	M/31	Impaired speech, tremor, peripheral neuropathy, CE, PN	Toxic serum level	1800	3.63	Tremor, dysphagia, dysarthria, peripheral neuropathy	
Apte and Langston,[38] 1983	M/38	Nystagmus, dysarthria, ataxia, choreoathetosis, impaired shortterm memory, CE, CA, CF	Suicide attempt, lithium intoxication, dehydration, oliguria	8100	5.70	Fever, impaired speech, coarse resting tremor, involuntary movements, masklike face, asterixis	
Apte and Langston,[38] 1983	F/50	Nystagmus, scanning speech, ataxia, dysmetria, choreoathetosis, CE, CA	Acute gastroenteritis	1200	2.80	Impaired short-term memory, ataxia	Tetracycline
Vredeveld and Morre,[71] 1983	F/77	Ataxia, CE			0.47–0.97	Ataxia, tremor	

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TABLE 2. *(continued)* Case Reports of SILENT in Published Literature (2004)

Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Donaldson and Cunningham,[52] 1983	F/53	Dysmetria, scanning speech, CE	Infection?	1000	3.90	Impaired speech, parkinsonian signs	Haloperidol, banztropine
Donaldson and Cunningham,[52] 1983	F/63	Dysarthria, resting tremor, ataxia, cerebellar atrophy, CE, CATR	Infection?	1000	1.90	Fever, disorientation, dysarthria, dysphagia, ataxia	Haloperidol, procyclidine hydrochloride
Lewis,[72] 1983	M/58	Buccolingual dyskinesia, EPS		1200	0.70–0.90	Ataxia, dysarthria, dysdiadochokinesis	Diazepam, desipramine
Manor,[73] 1983	F/28	Cerebellar choreoathetosis			3.9		
Mann et al,[74] 1983	M/39	Eye blinking, buccolinguomasticatory movements, facial tics, head nodding, choreoathetoid movements			1.07	Cogwheel rigidity	Haloperidol
Sandyk and Hurwitz,[46] 1983	F/42	Dementia, mutism, incontinence, ataxia, rigidity, frontal lobe signs		750	1.21	Rigidity, tremors, grand mal seizures, dysarthria, ataxia	Haloperidol
Sandyk and Hurwitz,[46] 1983	M/44	Unsteady gait, cogwheel rigidity, muscle weakness, dyskinesia		750	1.24	Confusion, ataxia, tremors, oculogyric crisis, dysarthria, myoclonus	
Zorumski and Bakris,[50] 1983	F/58	Choreoform movements		1200	1.2	Ataxia, dysarthria, confusion, choreoathetosis	
Green,[75] 1984	F/38	Ataxia, dysarthria, tremor		1200	2.06	Stupor, dysarthria, confusion, corticospinal tract signs	Thiothixene
Goswami et al,[76] 1984	M/55	Buccolinguomasticatory movements, cogwheel rigidity		1500	1.2	Restlessness, dysarthria, gait ataxia, cogwheel rigidity	Chlorpromazine
Lippmann et al,[77] 1985	M/41	Ataxia, dysarthria, CE	Suicide attempt, combination of therapy desmethyldoxepine		7.40	Comatose, myasthenialike presentation	In urine: amitryptiline, nortryptiline, doxepine, ethylalcohol
Addonizio,[78] 1985	M/25	Stiffness and persistent tremor, EPS	Neuroleptic–lithium combination	900	0.30	Stiffness in face, arms, legs, coarse parkinsonian tremor, rigidity	Chlorpromazine
Bejar,[79] 1985	M/23	Ataxia, dysarthria, cortical cerebellar atrophy	Overdose		8.0	Confusion, tremors, fever	
Izzo and Brody,[80] 1985	F/58	Ataxia, dysarthria, dysphagia			2.5	Unresponsive, focal seizures, rigidity, nystagmus	Haloperidol, furosemide, propranolol
Malhotra et al,[81] 1985, 1986	M/42	Cerebellar dysarthria, tremors, titubation, dysdiadochokinesis	Enteric fever	1500	0.85	Fever, tachycardia, gait ataxia	
Habib et al,[82] 1986	M/40	Cerebellar symptoms		750			Levopromazine, chlorpromazine, ampicillin
Habib et al,[82] 1986	F/61	Cerebellar symptoms, EPS		750	0.7		Haloperidol, biperiden, ampicillin
Jacome,[83] 1987	M/27	Dysarthria, ataxia, nystagmus, bilateral Babinski sign			1.5	Obtundation, rigiditiy, seizures	Haloperidol, diazepam
Teslo et al,[84] 1987	M/51	Ataxia, nystagmus, choreoathetosis, cerebellar atrophy, CE, CA, CATR	Suicide attempt and lithium intoxication	24,000	3.70	Lethargy, ataxia, seizures, stupor, hyperreflexia	Chlorpromazine
Ferbert and Czenik,[85] 1987	F/65	Ataxia, dysarthria, CE		900	2.60	Ataxia, tremor, bradydochokinesis, dysarthria	Thioridazine
Nagaraja et al,[86] 1987	M/35	Dyskinesia, CE, EPS, PN		600–2100	1.1	Confusion, ataxia, tremor	Chlorpromazine

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Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Nagaraja et al,[86] 1987	F/32	Dyskinesia, CE, EPS		600–2100	3.0	Coma, dehydration, fever	Chlorpromazine
Nagaraja et al,[86] 1987	M/32	CE, EPS	Dehydration, fever	900–1350	0.9	Confusion, dysarthria, ataxia	
Nagaraja et al,[86] 1987	F/33	CE, EPS		1650	0.4	Fever, confusion, ataxia	Chlorpromazine
Nagaraja et al,[86] 1987	M/41	Ataxia		900	0.7	Dysarthria, ataxia	
Nagaraja et al,[86] 1987	M/56	CE, EPS, PN		1200	0.7	Ataxia	Chlorpromazine, haloperidol
Andrade et al,[87] 1988	F/20	Persistent nystagmus, CE		900	0.45	Nystagmus, subclinical cerebral impairment, dysdiadochokinesis, ataxia, impaired coordination, extrapyramidal signs	
Saxena and Mallikarjuna,[88] 1988	M/21	Memory impairment, dysarthria, tremors	Overdose, suicide attempt	900	2.7	Dysarthria, tremors, vomiting, drowsiness, memory impairment	None
Adityanjee et al,[60] 1989	F/51	Dysarthria, ataxia, CE		800	1.70	Fever, slowed speech, coarse tremor, ataxia, dysarthria, dysdiadochokinesis, muscular incoordination	Propranolol
Adityanjee,[61] 1989	M/44	Dysarthria, gait ataxia, CE	Preexisting neurologic illness	1000	1.2	Fever, unresponsiveness, hypotonia, hemiparesis	
Verdoux and Bourgeois,[89] 1990	M/31	Ataxia, dysarthria, dysmetria, cerebellar atrophy, CE, CATR	Pyrexia	750	0.89	Vertical nystagmus, dysphagia, ataxia, dysarthria, hand tremor	Diazepam
Levine and Puchalski,[90] 1990	M/38	Chronic headache, left papilledema		1200	1.0	Monocular blindness, headache, nystagmus, papilledema	
Levine and Puchalski,[90] 1990	F/40	Visual blurring		900	0.9	Headache, nausea, vomiting, blurred vision, neck stiffness, tinnitus, nystagmus, papilledema	Fluphenazine, desipramine
Johnson et al,[91] 1991	F/69	Fasciculations, parathesias, PN	Dehydration	1000	1.89	Fever, unconsciousness, peripheral neuropathy, encephalopathy	
Swartz and Jones,[92] 1994	F/58	Unable to speak, unable to control urination	Rapid correction of hyperlithemia	1500	0.35	Stupor, incoherence, cogwheel rigidity, signs of dehydration	Trifluoperazine, synthroid, alprazolam, amitriptyline
Swartz and Jones,[92] 1994	F/54	Persistent memory retention deficits	Accidental overingestion	900	1.7	Jerking tremors, coma	Fluphenazine, aminophylline
Manto et al,[93] 1994	Adult	Cerebellar signs	Lithium toxicity along with hypernatremia			Cerebellar signs	None
Schneider and Mirra,[94] 1994	67/M	Persistent dysarthria and ataxia for 11 weeks followed by death, autopsy-neuronal loss and gliosis in cerebellar cortex, CE, CT	Acute lithium toxicity	2100	4.04	Encephalopathy and coma, dysarthia, muscular weakness, tremor, ataxia, hyperreflexia, drug interaction	Carbamazepine, perphenazine, hydralazine, verapamil, quinapril
Lecamwasam et al,[95] 1994	71/M	Encephalopathic illness with histologic evidence of neurologic sequelae	Chronic lithium toxicity	1500	0.88–0.99	Features of parkinsonism and dysphagia, dysarthria, deterioration in mobility, coma, generalized tremor	None
Mani et al,[28] 1996	F/24	Pronounced dysarthria and ataxia with brisk, deep tendon reflexes	Acute lithium toxicity with combination of lithium with antipsychotics	1000	0.8	Tremors, diarrhea, rigid extensor posturing, vertical nystagmus	Haloperidol

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TABLE 2. *(continued)* Case Reports of SILENT in Published Literature (2004)

Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Gille et al,[29] 1997	F/44	Persistent cerebellar syndrome	Combination of lithium with haloperidol, dehydration, hyperthermia		Therapeutic range	Acute encephalopathy	Haloperidol
Kores and Lader,[59] 1997	M/60	Ataxia, dysarthria, dysphagia		1250	3.9	Confusion, myoclonic jerks, dysarthria, truncal ataxia	
Kores and Lader,[59] 1997	F/61	Ataxia, dysarthria		800	2.2	Confusion, disorientation, ataxia, agitation, dysarthria	Naproxen
Kores and Lader,[59] 1997	F/29	Dysarthria		1200	1.67	Diarrhea, vomiting, incontinence, ataxia, dysarthria	
Kores and Lader,[59] 1997	F/71	Ataxia, dysarthria			2.63	Arrhythmia, tremor, dysarthria, ataxia	Diuretic, NSAID, trifluperazine
Kores and Lader,[59] 1997	F/64	Ataxia, dysarthria, dementia				Diarrhea, muscle twitching, dementia, impairment of consciousness	Haloperidol, diuretic, beta blocker, coproxamol, diclofenac
Kores and Lader,[59] 1997	F/45	Ataxia, dysarthria, dementia			3.6	Dehydration, confusion, ataxia	
Kores and Lader,[59] 1997	F/42	Ataxia, seizures			2.18	Agitation, infection, seizures, spastic quadriplegia	Erythromycin, haloperidol
Merle et al,[30] 1998	Adult	Persistent cerebellar syndrome	Combination with a neuroleptic				Neuroleptic
Normann et al,[31] 1998	M/62	Involuntary irregular choreoathetoid movements of muscles of upper limbs and trunk, perioral and finger movements	Lithium toxicity and combination with a neuroleptic	900	0.8	Severe delirium, extrapyramidal signs	Amitryptiline haloperidol, valproate
Brumm et al,[37] 1998	F/62	Cognitive sequelae including impaired memory, attention, executive control functions, visuospatial deficits, subcortical dementia	Severe lithium intoxication		3.9	Confusion, ataxia	Thiothexine, benztropine
Roy M. et al,[96] 1998	2 adult patients	Severe cerebellar atrophy	Lithium with a neuroleptic, dehydration, systemic infection, rapid correction of coexisting hyponatremia			Cerebellar signs	Neuroleptics
Biscof and Melms,[97] 1999	Adult	Persistent cerebellar deterioration	Lithium toxicity, lobar pneumonia		Therapeutic range		Carbamezapine, trifluperidol
Carcia–Resa et al,[98] 2001	Aged	Nonreversible neurotoxicity					
Lang and Davis,[25] 2002	M/44	Persistent cerebellar ataxia, extensor plantar response, poor balance	Insidious onset of lithium toxicity, hypertension, chronic renal failure, heart failure	1200	1.5mmol/l	Dysarthria, ataxia, leg weakness, shortness of breath	Amitryptiline, trifluperazine, aspirin, felodipine, verapamil
Bartha et al,[33] 2002	M/51	Praxis, impaired visuoperceptual functions	Acute lithium toxicity	1350	2.4	Psychomotor slowing, speech dysarthria, mood changes, incoherent discourse	None

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TABLE 2. *(continued)* Case Reports of SILENT in Published Literature (2004)

Author	Gender/ Age, y	Persistent Sequelae	Precipitating Factors	Dose, mg/d	Plasma Level, mM/L	Acute Neurologic Signs	Other Drugs
Fabisiak et al,[99] 2002	F/21	Blindness persisting for 4 months	Lithium toxicity leading to central pontine myelinolysis affecting the lateral geniculate bodies	1050		Extreme thirst, nausea, vomiting, diarrhea, poor coordination, facial paresis, blindness	None

BULB, bulbar; CA, choreoathetosis; CATR, cerebellar atrophy; CE, cerebellar; CF, cognitive functions; DE, dementia; EPS, extrapyramidal signs; MED, medullar; PN, peripheral neuropathy.

diuretics, β-blockers, coproxamol, and diclofenac[59]; and nonsteroidal antiinflammatory drugs.[59]

Psychiatric Diagnoses

Patients with schizoaffective disorders[19] and those with marked psychotic symptoms or anxiety features in the pretoxic period[49] may be more susceptible to lithium ion toxicity than most manic depressive patients. Among the recent cases included in our review, the most common diagnosis was bipolar disorder,[25,28,31,32,33,92,94,95,99] described by the various authors as "bipolar disorder,"[25,33,92,94,99] "manic depressive disorder,"[95] "bipolar disorder with severe mania and mild depression,"[31] "mania,"[32] and "manic depressive psychosis."[28]

Neurologic Status

Usually, high sensitivity or intolerance to lithium ions has been attributed to concomitant cerebral impairment.[18,55] Seizure-prone individuals, including those who had childhood febrile convulsions and Gillian–Barré syndrome may be more vulnerable to lithium-induced seizures even at therapeutic serum levels of lithium.[20,101] All 7 cases reported by Corcoran et al[2] had clinically advanced cerebral arteriosclerosis. Patients with baseline EEG abnormalities were found to have the most marked neurotoxicity and EEG changes with chronic lithium administration,[102] which is why studies have suggested lower doses and greater cautiousness in the progression of dosage in such patients.[22] Kelwala et al[103] found an accentuation of extrapyramidal symptoms in individuals with Alzheimer disease when put on lithium. A wealth of information suggests that individuals with preexisting neurologic illness or cerebral impairment are more likely to develop persisting sequelae after lithium intoxication, as well as more frequent acute intoxication.

Other Medical Factors

Infection, dehydration, deteriorating renal function, or the addition of other drugs to the regimen may precipitate acute toxicity.[52] Somatic illness preceded the intoxication in 11 of 40 cases reviewed by Schou.[54] Fever from any cause has been implicated in a large number of cases. The presence of high-grade fever in all 4 cases reported by Cohen and Cohen[36] has generated skepticism as to the typicality of the presentation.[54] The issue of its similarity to the neuroleptic malignant syndrome has been raised.[104] Although the clinical picture of NMS resembles that of chronic lithium intoxication, NMS is usually an acute condition and generally regresses without sequelae[104] (ie, although NMS sequelae have also been reported, they are not as common as SILENT). Adityanjee[104] suggests that because NMS is a descriptive term, superficial resemblance may be seen with any other descriptive syndrome (eg, lethal catatonia and SILENT), but this does not make them the same entity. Thus, the 4 cases reported by Cohen and Cohen[36] (Table 2) were likely not NMS, but rather fit the profile of SILENT, especially because they were all on very high doses of lithium carbonate for their age group.

Fever is thought to precipitate neurotoxicity in cases of SILENT.[17,52,53,81,86] If the temperature goes high enough, protein coagulation may take place anywhere in the central nervous system (CNS), and this could result in residual sequelae. Pathologic changes can be observed in the nerve cells and in glial cells in humans following mild-to-moderate thermal exposure.[105] Heat stress-induced hyperthermia, once believed to be nontoxic in the mammalian CNS, produces specific alterations in the CNS that may have long-term behavioral, physiologic, and neuropathologic consequences.[105] Heat stress affects cognitive performance differentially depending on the cognitive task, and a relationship exists between the effects of heat stress and deep body temperature.[106] A physiologically relevant increase in body temperature induces brain injury as well as a survival response to it, as demonstrated by the induction of hsp70 gene expression and activation of specific signaling pathways.[107] Hyperthermia causes HSF activation and the induction of hsp70 mRNA and protein to a greater extent in the cerebellum than in the hippocampus. Regional differences in the amount of white matter and in the cell types could explain the stronger heat-shock response of the cerebellum compared with the hippocampus.[107] Differential vulnerability to hyperthermia among various CNS loci may underlie the long-term physical sequelae post-NMS episode, because hyperthermia is an essential component of the NMS/malignant catatonia syndrome. Studies in several animal models and in humans suggest that heat can directly induce nervous tissue injury, and the severity of the insult depends on the level and duration of heating.[105] At extreme temperatures of 49 to 50°C in animal studies, all cellular structures are destroyed and cell death can be seen within 5 minutes.[105]

There is information available to suggest that fever, although playing a precipitating role, may also be an important manifestation of lithium neurotoxicity. Lithium-induced fever has been documented under laboratory conditions to be part of

the toxicity manifestations of the drug.[108] Schou et al[9] found that although the body temperature was normal during the initial stages of lithium poisoning, most of the patients developed pyrexia sooner or later during the comatose state. Hyperthermia produces hemoconcentration by increasing the fluid loss, resulting in higher serum levels of lithium, producing neurotoxicity.

Other putative precipitating factors for SILENT reported in the literature include hypertension, chronic renal failure, and heart failure[25]; the rapid correction of hyponatremia[96]; the rapid correction of hyperlithemia[92]; preexisting neurologic illness[45]; enteric fever[81]; acute gastroenteritis[50]; and epilepsy.[28]

Natural History

Mode of Onset

The signs and symptoms of lithium toxicity develop insidiously, and this may be erroneously interpreted as a mild depressive episode in the patient. Usually, it is only when the patient develops florid signs that the diagnosis of lithium toxicity is considered. It is likely that the use of sustained-release preparations may contribute to toxicity because, although these preparations used in single daily doses have traditionally been considered quite safe and convenient,[109] at least in some of the cases they may not serve this purpose.[110] The absorption of these slow-release preparations has been found to be quite erratic[111] and, especially if given in a single daily dose, can erratically lead to very high lithium concentrations.[110]

Symptom Progression

Leukocytosis in the absence of infection is a recognized effect of lithium therapy[112] and WBC counts more than 10,000 cells/mm^3 have been reported earlier.[36,52,65] The WBC count gradually comes back to normal as soon as the acute phase is over. Schou[54] maintains that acute intoxications precede the sequelae in all cases, and that the acute phase is without cerebellar symptoms, and as consciousness returns, the neurologic sequelae become apparent. Although this is usually the case, exceptions do occur. There have been reports of patients who had cerebellar signs present from the beginning of the acute phase.[28,35,36,46,59,75,93,96] Donaldson and Cunningham[52] reported extrapyramidal symptoms from the beginning of the acute phase, although cerebellar dysfunction became apparent only when patients were more cooperative.[52] Initial symptoms are decreased alertness or slight apathy, followed by muscular rigidity or muscular fasciculations with varying localization and slight ataxia.[32,53,59,95] The symptoms worsen gradually and are followed by impaired consciousness, more severe fasciculations, coarse tremors of the limbs, and worsening ataxia. The severest state of lithium intoxication is characterized by a stuporlike impairment of consciousness or "coma vigil."[53,94]

Although this sequence of events is typical of acute lithium intoxication, even in patients with long-lasting sequelae, at least initially, a similar picture is observed. Later on, as consciousness is regained, signs and symptoms hitherto disregarded may be observed or may even increase progressively. The same progression has been suggested regarding peripheral neuropathy.[44]

TABLE 3. SILENT Clinical Profile

Typical presentations

1. Persistent cerebellar dysfunction
2. Persisting extrapyramidal syndromes
3. Persisting brainstem dysfunction
4. Dementia with varying degrees of organic mental syndromes

Presentation	Ref.
Atypical Presentations	
Downbeat nystagmus	39
Retrobulbar optic neuritis	40
Persistent papilledema	41
Choreoathetoid movements	31, 50
Peripheral neuropathy (both motor and sensory)	43, 44, 67, 113
Myopathy	64
Blindness (due to central pontine myelinolysis)	99

Course and Prognosis

Considering the persistence of sequelae 2 months beyond the cessation of lithium as a criterion,[54] some cases without any acute confusion/stupor may still be regarded as long-lasting neurologic sequelae.[39–42] A few of these had earlier episodes of acute lithium toxicity that responded either to a dose reduction or to stoppage of treatment. Notwithstanding the initial picture, the neurologic sequelae persist for varying time intervals beyond 2 months after cessation of lithium, occasionally being reported as long as 5 years after cessation.[34] In most of the published cases sequelae were still persistent, albeit lesser in severity, at the 1-year follow-up.

Clinical Presentations

In our review of the literature, we found a varied presentation for cases of SILENT (Table 3), from the typical signs of cerebellar dysfunction to atypical presentations like central pontine myelinolysis (CPM) and retrobulbar optic neuritis. Fabisiak et al[99] described a case of CPM manifested by temporary blindness that persisted for 4 months. They suggest that the CPM was due to lithium toxicity affecting the lateral geniculate nucleus, producing blindness. Cognitive deficits due to lithium toxicity were reported in at least 1 separate publications.[33,32] Bartha et al[33] described a case with prolonged apraxia and impaired visuoperceptual functions, and Brumm et al[32] described a case with prolonged memory deficits and subcortical dementia. These cases represent persistent cognitive defects with lithium, presenting as subcortical dementia, and highlight the neuropsychological sequelae of lithium intoxication. Lang and Davis[25] described a case of persistent cerebellar ataxia and positive Babinski sign. A case of a bipolar patient reported by Normann et al[31] described delirium and dyskinesia. Although the delirium was reversible after cessation of the lithium–neuroleptic combination, the dyskinesia persisted for 6 months. Kores and Lader[59] presented the vignettes of 7 cases fitting the profile of SILENT. Six of them had persistent ataxia, 6 had persistent dysarthria, and 5 had both. Lecamwasam et al[95] described a case of

chronic lithium neurotoxicity presenting as an encephalopathic illness, with histologic evidence of neurologic sequelae. Swartz and Jones[92] described 2 cases fitting the profile of SILENT. One of them had persistent inability to speak and control urination; the other had slight memory deficits. Apart from the typical presentations of persistent cerebellar dysfunction, extrapyramidal syndromes, brainstem dysfunction, and dementia, there are atypical presentations of SILENT (Table 3) reported. Theses include a case of optic neuritis,[40] CPM,[99] papilledema,[41] and choreoathetoid movements,[31,50] among others (see Table 3 for complete list). All these patients (typical and atypical presentations) continued to have symptoms and signs for more than 2 months after the cessation of lithium, and this was 1 of the criteria arbitrarily laid down by Schou[54] for defining the after-effects as persistent.

The profile of the after-effects may follow any of the patterns or varying combinations mentioned in Table 2, and described briefly previously. Those with atypical presentations are unlikely to have undergone an acute organic brain syndrome, a fact that has not been appreciated until now. For example, a patient who developed papilledema following therapeutic doses of lithium carbonate initially complained only of bilateral blurring of vision.[41] The papilledema did not completely disappear after cessation of lithium, and was treated with steroids. The funduscopic abnormalities continued to persist for 2.5 years after the cessation of lithium. Another case, a patient who had been on lithium for the previous 10 years, developed bilateral retrobulbar optic neuritis that regressed after cessation of lithium.[40] Four cases of peripheral neuropathy reported were confirmed on nerve conduction studies and nerve biopsy.[43,44,67,113] The only case of myopathy seen in combination with cerebellar dysfunction was confirmed on EEG and muscle biopsy.[64] Downbeat nystagmus alone without any acute intoxication[39] and choreoathetoid movements in the absence of any other features[50] persisted for more than 2 months after the cessation of lithium, although the patients recovered completely afterward.

As described earlier, and as seen in Table 2, the gamut of presentations is rather diverse. Nevertheless, the essential common features remain (1) causation of these neurologic dysfunctions by lithium carbonate in the absence of prior neurologic illness and (2) the persistence of the sequelae for varying periods beyond 2 months after the cessation of lithium. They may persist for extremely long periods and, for all practical purposes, may be irreversible. It is desirable that a descriptive term be coined for this potentially serious and, in some cases, irreversible condition, with the stated purpose of conveniently identifying, describing, and treating it.

Mechanism/Etiopathogenesis

The putative biologic mechanism of SILENT is still far from clear; however, extensive demyelination has been found on biopsy, in the peripheral nerves involved.[44,56,67,113] It is probable that even in the CNS, demyelination at multiple sites, especially involving the cerebellum,[56] may be responsible for the persistence of neurologic after-effects, loss of Purkinje cells,[95] gliosis of the cerebellar cortex,[94] and cerebellar atrophy. The molecular basis for the therapeutic actions of lithium and its effect on gene expression has been extensively studied and is not the focus of the current review.[114–117]

Management

Irreversible damage, once sustained, is rather difficult to treat. Some of the cases do show spontaneous recovery that may be total, but in others, sequelae continue to persist. The abrupt discontinuation of lithium may also lead to sequelae.[26] Rapid correction of hyperlithemia poses neurotoxic risks.[92] Some helpful measures include the avoidance of acute intoxications with lithium, long-term and continuous dose adjustment and serum level monitoring, stricter exclusion criteria for starting lithium, and prompt and aggressive treatment of acute lithium neurotoxicity with prolonged sessions (lasting more than 12 hours) of hemodialysis, as advocated earlier.[35,38,45,53] In case hemodialysis is not available, peritoneal dialysis should be resorted to.[53]

Management of Long-Term Sequelae

Once the long-term neurologic sequelae have set in, the patient should be managed according to the impediment (eg, physical rehabilitation for gait ataxia, speech training for dysarthria, and cognitive training for dementia and memory impairments).

Preventive Approach

Because the therapeutic range of lithium approximates very closely to toxic levels,[15] recent practices of using lower lithium dosages and serum lithium levels especially for maintenance treatment[56,118,119] may go a long way in reducing the incidence of SILENT, albeit at the risk of higher relapse/recurrence rates. Patients with concomitant medical conditions like impaired renal function, and those on other drugs may need special attention. In addition, the age of a patient should be taken into account when prescribing lithium, because older individuals have a decreased creatinine clearance and a lower glomerular filtration rate. Consequently, the drug may achieve higher serum levels even at nominal doses.

FUTURE RECOMMENDATIONS

The long-term sequelae of lithium intoxication are an important clinical issue. It is important to raise the awareness of this condition so that clinicians may better be able to avoid it. The only way to decrease the occurrence of these sequelae is by increasing awareness. Also, it is important to define properly the syndrome/condition with a descriptive term, to elucidate the condition clearly, and to avoid wide differential diagnoses.

There have been recent advances in the understanding of the molecular basis of neurotoxicity, including lithium-induced neurotoxicity. Lenox and Wang[116] suggest that the signaling pathways in the nervous system offer an opportunity to replicate signals critical for altering gene expression, which is the underlying mechanism for the adaptive response of neurons to chronic lithium exposure. By linking lithium-responsive genes as a regulatory network, researchers may be able to provide a means to define a pathway associated with the long-term prophylactic properties of lithium, distinct from its toxicity profile. This identification of gene expression

patterns that distinguish between therapeutic and toxic actions of lithium may help in the discovery of new drugs for mood stabilization.

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