REVIEW
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The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity: A Scoping Review

ABSTRACT

The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) is a rare but concerning neurological complication resulting from lithium intoxication. Despite being reported since the 1960s, SILENT remains poorly understood and previous reviews on this topic commonly have been narrative. We therefore conducted a scoping review to assess the nature and scope of the research literature on the long-term neurological sequelae of lithium toxicity and determine the current knowledge of SILENT. A comprehensive and systematic literature search, using the MEDLINE, Embase, and Web of Science databases (from inception to July 2023), was conducted for English and Dutch articles, assessing the long-term neurological sequelae of lithium intoxication. Key information concerning clinical manifestations, risk factors, therapeutic approaches, or preventive measurements was extracted. We reviewed 91 articles, extracting information from 117 cases of SILENT. The prevailing outcome observed was persistent cerebellar dysfunction (77% of cases), often in combination with other sequelae. Other common sequelae included cognitive problems, parkinsonism, choreoathetosis, tardive dyskinesia, and peripheral neuropathy. The most common (61.4%) acute neurological symptom in the development of SILENT is an altered level of consciousness ranging from confusion to comatose states. Cerebellar sequelae were mentioned in 77% of cases as most common persistent sequelae. Antipsychotic use was mentioned in 59% of cases and fever was reported in 37.6% of cases. Scientific knowledge about this phenomenon has not advanced much since its initial reports in the 1960s and 1970s. While the use of lithium has become much more stringent than it had been in years past, and the occurrence of SILENT is rather exceptional, raising awareness about SILENT nevertheless remains crucial to avoid deleterious neurological consequences. Comprehensive, high-quality research in a systematic and standardized manner is therefore urgently needed to better understand this phenomenon.

Keywords: Lithium, neurotoxicity, neurological sequelae, affective disorder

Introduction

Since the 1950s, lithium has been introduced as a therapeutic intervention for managing recurrent depressive episodes. Subsequently, it received approval and gained widespread recognition as the benchmark treatment for adult patients with bipolar disorder, as it has also been found efficacious in the acute and maintenance treatment of bipolar disorder since 1970. Last, extensive scientific research has demonstrated the efficacy of lithium as an augmenting agent in cases of antidepressant non-responsiveness or treatment-resistant major depression.[1–5]

Lithium has a relatively narrow therapeutic index and needs careful dose titration with follow-up of clinical neuropsychiatric side effects, concomitant with monitoring of lithium serum levels. Lithium toxicity is a common clinical problem that can be acute, "acute on chronic", or chronic. Most of these symptoms are reversible by dose reduction, interruption, or treatment withdrawal.[2] Over the last 50 years, however, there have been occasional reports in the literature of permanent (irreversible) neurological damage following lithium treatment, even without toxic serum concentrations or after discontinuing treatment. This serious adverse event was first described by Verbov in 1965,[6] after which several other case reports appeared

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in the 1970s. In 1984, Schou introduced the definition of this complication as "a long-lasting neurological sequelae for over two months after discontinuing lithium treatment".[7]

Later Adityanjee[8] coined the descriptive acronym SILENT (syndrome of irreversible lithium-effectuated neurotoxicity).[8]

Although there have been some reviews on this topic in the past, they were all narrative.[7,9–11] Recently, Verdoux et al[12] published a systematic review but limited their research question to the role of fever in the occurrence of neurological sequelae following lithium intoxication.[12] We therefore conducted a scoping review to assess the nature and scope of the research literature on the long-term neurological sequelae of lithium intoxication and determine the present current knowledge of SILENT. More specifically, we wanted to explore (1) the clinical manifestations of SILENT; (2) risk factors for the development of SILENT; (3) therapeutic approaches and preventive measures; and (4) whether clinical knowledge on this syndrome increased over the last 20 years.

Material and Methods

This scoping review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses, extension for scoping reviews (PRISMA-ScR).[13]

Search Strategy

A comprehensive and systematic literature search, using the MEDLINE (via PubMed), Embase, and Web of Science databases (from inception to July 2023) was conducted for English and Dutch articles, assessing the long-term neurological sequelae of lithium intoxication, presenting data on the clinical manifestations, risk factors and/or therapeutic approaches, or preventive measurements. One of the authors (J.D.), an experienced biomedical information specialist, constructed effective search strings for the different databases. Duplicates were removed using EndNote X9 (J.D.). After removing duplicates, titles and abstracts were screened by K.K., using Rayyan QCRI. K.K. reviewed the full text of the selected articles and assessed their eligibility. Articles that were deemed potentially relevant according to the selection criteria were included. Any disagreements were solved by consensus or by decision of the other reviewers (J.D. and F.B.). K.K. also attempted to identify additional studies by using the reference list of potentially relevant reports and articles.

Selection Criteria

Inclusion Criteria: Articles were included if they met the following inclusion criteria: (1) English or Dutch published, peer-reviewed articles; (2) in- or outpatients of any age and psychiatric diagnosis without pre-existing neurological disease; (3) patients who took lithium and suffered from persistent neurological sequelae for at least 2 months after the cessation of the medication; (4) All study designs were eligible for inclusion if they provided additional cases.

Exclusion Criteria: Articles published in languages other than English or Dutch, grey literature (such as posters, conference abstracts/papers, dissertations, and website articles), studies or case-reports including patients with a follow-up period shorter than 2 months after withdrawal of the medication (this also included cases where fatal outcomes occurred within 2 months of treatment discontinuation), or cases without specifying a time frame following lithium discontinuation, were excluded.

Data Extraction

Data was extracted and mapped descriptively by K.K., using a data extraction form. This form included the following information:

(1) author and publication year; (2) age and gender; (3) nature of the neurological sequelae observed; (4) acute neurologic signs; (5) precipitating factors; (6) lithium dose (mg/day); (7) lithium maximum plasma level (mM/L); (8) co-prescribed drugs (antipsychotics and other medications).

Results

Selection Process

The initial search across the 3 databases yielded a total of 2903 reports (see Figure 1 for the PRISMA-ScR flowchart). Of these, 1149 duplicate reports were removed. Overall, 142 articles studies were selected as potentially eligible, of which 61 original records met the inclusion criteria. Thirty articles[6,14–42] were added by cross-reference, making a total of 91 articles. All included articles were case reports, except for 2 reviews,[10,11] including a total of 117 SILENT cases.

General Study Characteristics

The highest number of case reports is concentrated in the 1980s, with only a relatively small number occurring in the last 20 years. (1960s: n = 1; 1970s: n = 18; 1980s: n = 38; 1990s: n = 25; 2000s: n = 16; 2010s: n = 10; 2020s n = 9). The majority of articles documented a solitary case (n = 77, 85%). Ten articles documented 2 cases (11%), 1 three cases (1%), 1 four cases (1%), and 1 six cases (1%). The highest number of cases documented in a single article was 7 (1%).

Although 5 cases did mention existing neurological disease, they were ultimately included in the final review because of their indeterminate character.[43–47]

Patient and Treatment Characteristics

Even though we identified a total of 117 cases, not all of them provided complete information on all specific parameters. Hence, the mean and standard deviation (SD) for each parameter are based on varying numbers of observations.

Gender: There were 56% (n = 65) female patients and 44% (n = 52) male patients [mean years: 48.1; SD: 13.85; range: 15-72, with 14 cases (12%) aged ≥65 ('geriatric')].

Doses and Serum Levels of Lithium Treatment: Reported serum levels (n = 106) ranged from 0.25 mM/L to 8 mM/L (mean: 2.37 mM/L; SD: 1.55 mM/L).

MAIN POINTS

- *The syndrome of irreversible lithium-effectuated neurotoxicity is underreported, often misinterpreted, and misdiagnosed.*
- *Case reports without an acute lithium intoxication are rare.*
- *The initial phase is characterized by an altered level of consciousness followed by a cerebellar syndrome.*
- *Further research is needed as knowledge about this syndrome has not advanced much since initial reports.*

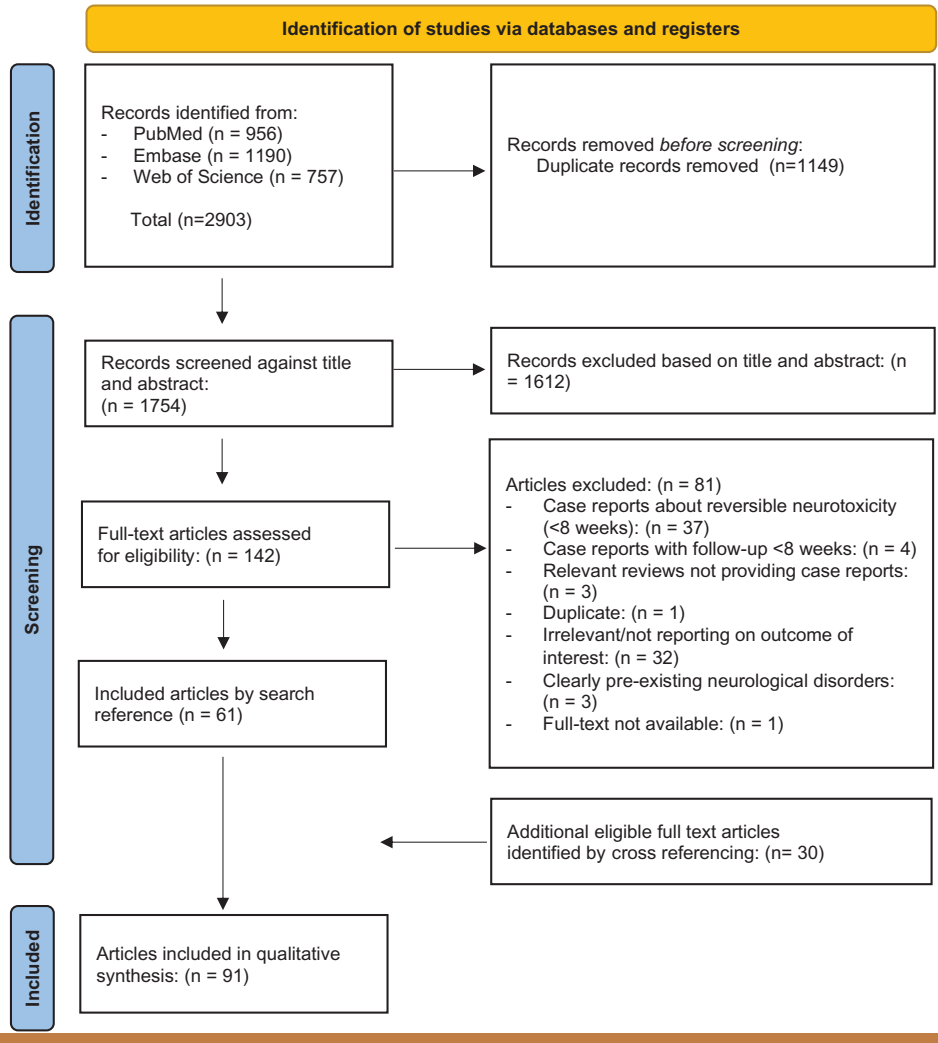

Figure 1 . Preferred reporting items for systematic reviews and meta-analyses flow diagram.

Eighty one reports provided data on drug toxicity. Excluding overdose cases (n = 14), dose levels at which toxicity occurred varied from 438 mg/day to 2800 mg/day (mean dose: 1194 mg/day, SD: 465 mg/day, median 1200 mg/day, interquartile range 900-1500). Employing the Extracorporeal Treatments In Poisoning (EXTRIP) classification,[48] the distribution of maximum lithium levels is as follows: (i) no toxicity <1.5 mM/L n = 34 (32.1%); (ii) mild toxicity 1.5-2.5 mM/L n = 27 (25.5%); (iii) moderate toxicity 2.5-3.5 mM/L n = 23 (21.7%); (iv) severe toxicity >3.5 mM/L n = 22 (20.8%).

Drug Combinations: There were 41 (35%) cases where no other (psychotropic nor non-psychotropic) medication use was mentioned.

In 59% (n = 69) of the cases, antipsychotic use was mentioned, with 78.3% (n = 54) being a first-generation antipsychotic (FGA) and 21.7% (n = 15) a second-generation antipsychotic (SGA). In total, we documented 11 different FGA and 4 different SGA molecules. The most frequently reported co-prescribed FGA was haloperidol, followed by chlorpromazine. Among the SGA, olanzapine was the most frequently reported.

Other co-prescribed psychotropic medications included tricyclic antidepressants (TCAs) (n = 11), selective serotonin reuptake inhibitors (SSRIs) (n = 4), antiepileptics (n = 10), and anticholinergics/antihistamines. The indication for antiepileptic drugs was not always specified. Given the type of psychiatric conditions presented, we suppose that these medications were used as mood stabilizers. Other non-psychotropic medications can be found in Table 1.

Associated Medical Factors: Fever was mentioned in 44 cases (37.6%), for which the etiology was not specified in 27 cases. Infection was mentioned in 14 cases (but 4 of them did not indicate whether fever was present). For 6 of these cases fever was associated with neuroleptic malignant syndrome (NMS) and in 1 case with heatstroke.

Other medical conditions mentioned were dehydration, anorexia, alcohol abuse/intoxication, surgery, and diabetes insipidus.

Clinical Manifestations of SILENT: There was considerable variability in the reporting of neurological symptoms or syndromes. The manner of description also differed between acute neurological signs and persistent sequelae. For the acute signs, descriptions often employed symptom-based terminology (e.g. ataxic gait), while for persistent

Table 1. Case Reports of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity in Published Peer Reviewed Literature

Author and Publication Year	Age/ Gender	Nature of Persistent Sequelae	Acute Neurologic Signs	Precipitating Factors	Lithium Dose (mg/day)	Lithium Maximum Plasma Level (mM/L)	Co-Prescribed Drugs	
							Antipsychotics	Other Drugs
Verbov et al, 1965[6]	51/F	Cerebellar	Comatose, spasticity, plantar reflex	Fever, anorexia	1000		Chlorpromazine	
Von Hartitzsch et al, 1972[49]	50/F	Cerebellar, choreoathetosis, plantar reflex	Lethargy, ataxia, seizures, stupor, hyperreflexia, plantar reflex, coma		1600	5.0	Chlorpromazine	
Von Hartitzsch et al, 1972[49]	53/F	Cerebellar, choreoathetosis, plantar reflex	Disorientation, ataxia, coarse tremor, seizure, stupor, hyperreflexia, plantar reflex		1600	2.3		
Juul-Jensen and Schou, 1973[42]	38/F	Cerebellar	Bilateral nystagmus, spasticity, hyperreflexia, myoclonus, seizures		Overdose (intentional)	5.6		Phenytoin
Juul-Jensen and Schou, 1973[42]	55/F	Cerebellar	Tremor, rigidity, impaired consciousness	Dehydration, surgery	900	2.9		
Cohen & Cohen, 1974[41]	34/F	Cerebellar, dementia, EPS	Confusion, tremor, cogwheel rigidity, stupor, involuntary movements, dysarthria, ataxia, vertical nystagmus	Fever	1800	1.81	Haloperidol	Benztropine
Cohen & Cohen, 1974[41]	40/F	Cerebellar, EPS, medullar	Somnolence, tremor, muscular rigidity, ataxia, vertical nystagmus, dysarthria	Fever	1500	1.48	Haloperidol	Benztropine
Cohen & Cohen, 1974[41]	63/F	Cerebellar, choreoathetosis, EPS	Impaired consciousness, tremor, cogwheel rigidity, ataxia	Fever	1165	1.58	Haloperidol	Benztropine
Cohen & Cohen, 1974[41]	63/F	Cerebellar, choreoathetosis, EPS	Tremor, dysarthria, mask face, postural tremor, lethargy, rigidity	Fever	1800	2.45	Haloperidol	
Johnson, 1976[50]	50/F	Cerebellar, bulbar, medullar	Ataxia, slurred speech, fluctuating consciousness			3.0		
Goldwater & Pollack, 1976[40]	57/F	Cerebellar, cognitive deficits	Tremor, mask face, confusion, mouthing movements, clasp knife spasticity, cogwheel rigidity, hyperreflexia, plantar reflex, oculogyric crisis, ophisthotonic attacks		438	4.8		Phenytoin
Hansen and Amdisen, 1978[51]	65/M	Dementia	Stupor	Dehydration	32 (mmol/ day)	2.1		
Hansen and Amdisen, 1978[51]	63/F	Cerebellar, dementia	Stupor		24 (mmol/ day)	3.15		
Lobo et al, 1978[39]	29/F	Papilledema	Blurred vision, papilledema, nonspecific difficulties with eyes		1800	1.2		
Julien et al, 1979[52]	62/F	Cerebellar			1000	2.69		
Newman and Saunders, 1979[43]	47/M	Cerebellar, paraplegia	Ataxia, spastic paraplegia, mental deterioration, stupor	Multiple sclerosis (?)		2.3		

(*Continued*)

Table 1. Case Reports of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity in Published Peer Reviewed Literature (*Continued*)

Author and Publication Year	Age/ Gender	Nature of Persistent Sequelae	Acute Neurologic Signs	Precipitating Factors	Lithium Dose (mg/day)	Lithium Maximum Plasma Level (mM/L)	Co-Prescribed Drugs	
							Antipsychotics	Other Drugs
Newman and Saunders, 1979[43]	42/F	Axonal neuropathy	Coma, flaccid paralysis, absent tendon reflexes and plantar responses, proximal muscle weakness			1.9		
Thomas, 1979[38]	58/F	Dementia	EPS, TD, confusional state, disorientation				Haloperidol	
Warick, 1979[37]	36/M	Cerebellar	Obtunded sensorium, coarse tremors, ataxic, lethargic, uncommunicative, incontinent, plantar reflex	Infection, dehydration, alcohol abuse	2700	7.6		Clorazepate, sulfamethoxazole
Sampath et al, 1980[53]	22/M	Cerebellar (dysarthria)	Drowsy, confused, irritable, memory deficits, coarse tremor, dysarthria, moderate weakness and hypotonia in all limbs, mild ataxia and nystagmus, symmetric diminished reflexes		1050	1.0		None
Peiffer, 1981[54]	61/F	Cerebellar, parkinsonism, slight dementia	Bursts of perspiration, kinetic restlessness, chewing movements, slurred speech, uncoordinated fiddling movements, non-responsive, hyperreflexia	Fever	1668	2.02	Perazine	
Baker et al, 1981[36]	37/M	Cerebellar	Delirium, dysarthria, nystagmus	Fever (legionnaire disease = pneumonia)	2400	1.2	Haloperidol	Benztropine, diphenhydramine and secobarbital
Pringuey et al, 1981[35]	54/M	Cerebellar		Dehydration	1500	3.8		Digitalis
Spring and Frankl, 1981[34]	53/M	Cerebellar, EPS	Cogwheeling, stupor, parkinsonian gait	Fever	2400	1.5	Haloperidol	Benztropine, diphenhydramine
Uchigata et al, 1981[33]	56/M	Cerebellar, peripheral neuropathy	Drowsiness, dysarthria, muscle twitching, unsteady gait, rigidity	Fever	1800	1.4	Chlorpromazine, levomepromazine	
Sellers et al, 1982[55]	43/F	Cerebellar	Unconsciousness, rigidity, tremor, opisthotonos, ataxia, dysarthria, nystagmus		750	2.5	Chlorpromazine, thioridazine	
Pamphlett and Mackenzie, 1982[32]	31/M	Cerebellar, peripheral neuropathy	Confusion, weakness, and tremulousness		1800	3.63		
Singh, 1982[31]	36/F	Cerebellar	Confusion, ataxia, dysarthria, coarse tremor		1200	0.25	Fluphenazine	
Donaldson and Cunningham, 1983[10]	53/F	Cerebellar	Impaired speech, parkinsonism	Fever	1000	3.9	Haloperidol	Benztropine

(*Continued*)

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							Antipsychotics	Other Drugs
Donaldson and Cunningham, 1983[10]	63/F	Cerebellar	Disorientation, dysarthria, dysphagia, ataxia	Fever	1000	1.9	Haloperidol	Procyclidine, hydrochloride
Manor, 1983[56]	28/F	Cerebellar, choreoathetosis				3.9		
Mann et al, 1983[57]	39/M	Facial dyskinesia (TD), choreoathetosis	Cogwheel rigidity			1.07	Haloperidol	
Sandyk and Hurwitz, 1983[58]	42/F	Dementia, cerebellar, EPS, frontal lobe signs, choreoathetosis	Rigidity, tremors, seizures, dysarthria, ataxia	Subfebrile	750	1.21	Haloperidol	
Sandyk and Hurwitz, 1983[58]	44/M	Cerebellar, facial dyskinesia (TD)	Confusion, ataxia, coarse tremors, oculogyric crisis, dysarthria, myoclonus		750	1.24	Haloperidol	
Lewis, 1983[59]	58/M	Facial dyskinesia (TD)			1200	0.9		Diazepam, desipramine
Apte and Langston, 1983[30]	38/M	Cerebellar, choreoathetosis, cognitive deficits	Impaired speech, coarse tremor, involuntary movements, masklike face, asterixis	Fever, dehydration	8100 (intentional overdose)	5.7		
Apte and Langston, 1983[30]	50/F	Cerebellar, choreoathetosis	Impaired short term memory, ataxia	Infection, alcohol abuse	1200	2.8		Tetracycline
Zorumski and Bakris, 1983[29]	58/F	Choreoathetosis	Ataxia, dysarthria, confusion, choreoathetosis		1200	1.2		
Green, 1984[28]	38/F	Cerebellar	Stupor, dysarthria, confusion, corticospinal tract signs		1200	2.06	Thiothixene	
Bejar, 1985[60]	23/M	Cerebellar	Confusion, coarse tremors, agitation, nausea and emesis	Fever	12000 (intentional overdose)	8.0		
Izzo and Brody, 1985[61]	58/F	Cerebellar	Unresponsive, focal seizures, rigidity, nystagmus			2.5	Haloperidol	Furosemide, propranolol
Lippmann et al, 1985[27]	41/M	Cerebellar	Comatose, myasthenia like presentation		Polypharmacy intentional overdose	7.4		Amitriptyline, nortriptyline, doxepin, ethylalcohol
Malhotra et al, 1985[26]	42/M	Cerebellar	Tachycardia, gait ataxia	Fever (infection)	1500	0.85		
Pheterson et al, 1986[25]	38/F	Cerebellar, subcortical dementia	Semi comatose state	Fever (infection)		2.4		Amitriptyline
Andrade et al, 1987[44]	20/F	Cerebellar (nystagmus)	Nystagmus, confusion, disorientation, cerebellar, EPS	Moderate mental retardation (?)	900	0.5		
Jacome, 1987[62]	27/M	Cerebellar, plantar reflex	Obtundation, rigidity, seizures			1.5	Haloperidol	Diazepam

(*Continued*)

Table 1. Case Reports of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity in Published Peer Reviewed Literature (*Continued*)

Author and Publication Year	Age/ Gender	Nature of Persistent Sequelae	Acute Neurologic Signs	Precipitating Factors	Lithium Dose (mg/day)	Lithium Maximum Plasma Level (mM/L)	Co-Prescribed Drugs	
							Antipsychotics	Other Drugs
Nagaraja et al, 1987[63]	35/M	Cerebellar, EPS, peripheral neuropathy	Confusion, ataxia, tremor		2100	1.1	Chlorpromazine	
Nagaraja et al, 1987[63]	32/F	Cerebellar, EPS	Coma	Dehydration, fever	2100	3.0	Chlorpromazine	
Nagaraja et al, 1987[63]	32/M	Cerebellar, EPS		Dehydration, fever	1350	0.9		
Nagaraja et al, 1987[63]	33/F	Cerebellar, EPS	Confusion, ataxia	Fever	1650	0.4	Chlorpromazine	
Nagaraja et al, 1987[63]	41/M	Cerebellar	Dysarthria, ataxia		900	0.7		
Nagaraja et al, 1987[63]	56/M	Cerebellar, EPS, peripheral neuropathy	Ataxia		1200	0.7	Chlorpromazine, haloperidol	
Tesio et al, 1987[64]	51/M	Cerebellar, choreoathetosis	Lethargy, ataxia, seizures, stupor, hyperreflexia	Alcohol intoxication	24000 (intentional overdose)	3.7	Chlorpromazine	Lorazepam
Yoshimoto, 1987[65]	56/M	Cerebellar	Drowsiness, dysarthria, tremor, rigidity, coma	Fever	1800			
Van Den Broek et al, 1988[66]	72/F	Hypokinetic rigid syndrome with TD	Soporous, episodic profuse transpiration, disorientation, hypertonia, rigidity, plantar reflex	Fever	1200	0.9	Haloperidol	
Saxena and Mallikarjuna, 1988[24]	21/M	Cognitive deficits	Dysarthria, tremors, drowsiness, memory impairment		15000 (intentional overdose)	2.7		
Adityanjee, 1989[67]	51/F	Cerebellar	Slowed speech, coarse tremor, ataxia, dysarthria, dysdiadochokinesia, incoordination	Fever	800	1.7		Propranolol
Van Scheyen, 1990[68]	68/F	Dementia	Reduced consciousness, agitation, EPS, choreoathetosis, disorientation, cerebellar		600	0.7	Haloperidol	
Verdoux and Bourgeois, 1990[69]	31/M	Cerebellar	Vertical nystagmus, dysphagia, ataxia, dysarthria, coarse tremor	Fever, alcohol abuse, NMS	750	0.89		Diazepam
Levine and Puchalski, 1990[23]	38/M	Papilledema (left eye)	Monocular blindness, headache, nystagmus		1200	1		
Levine and Puchalski, 1990[23]	40/F	Visual blurring	Headache, nausea, blurred vision, tinnitus, nystagmus, papilledema		900	0.9	Fluphenazine	Desipramine
Johnston et al, 1991[22]	69/F	Peripheral neuropathy	Unconsciousness, encephalopathy, peripheral neuropathy	Fever, dehydration	1000	1.89		

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							Antipsychotics	Other Drugs
Khanna and Sethi, 1993[70]	15/M	Cerebellar, EPS	Masked faces, sialorrhea, cogwheel rigidity, dysarthria, ataxia, dysmetria, dysdiadochokinesia, intention tremor, dysphasia, paresis of tongue	Fever	750	0.4	Haloperidol	
Schneider and Mirra, 1994[71]	67/M	Cerebellar	Encephalopathy and coma, dysarthria, muscular weakness, tremor, ataxia, hyperreflexia		2100	4.04	Perphenazine	Carbamazepine, verapamil, quinapril, hydralazine
Swartz and Jones, 1994[72]	54/F	Cognitive deficits	Jerking tremors, coma		1200	6.3	Fluphenazine	Aminophylline
Swartz and Jones, 1994[72]	58/F	Brainstem lesion, cognitive deficits	Stupor, cogwheel rigidity	Dehydration, fever	1500	3.4	Trifluoperazine	Amitriptyline, alprazolam, L-thyroxine
Borggreve et al, 1995[73]	59/F	Cerebellar, cognitive deficits	Somnolence, incoherence, disorientation, dysarthria, generalized myoclonia		800	3.2		Carbamazepine
Mani et al, 1996[74]	24/F	Cerebellar	Tremors, diarrhea, lethargy, rigid extensor posturing, vertical nystagmus		1000	0.8	Haloperidol, chlorpromazine	
Khan et al, 1997[75]	63/M	Cerebellar, EPS, cognitive deficits, (CPM)	Lethargy, confused, bedridden, mute, brisk tendon reflexes, blepharospasm, positive glabellar reflex	Diabetes insipidus	300	1.5	Fluphenazine, amantadine	Triamterene/ hydrochlorothiazide
Kores and Lader, 1997[11]	60/M	Cerebellar	Confusion, myoclonic jerks, dysarthria, vomiting, sweating, truncal ataxia		1250	3.9		
Kores and Lader, 1997[11]	61/F	Cerebellar	Confusion, disorientation, ataxia, agitation, dysarthria	Dehydration	800	2.2		Naproxen, paracetamol/dihydrocodeine
Kores and Lader, 1997[11]	29/F	Cerebellar	Diarrhea, vomiting, incontinence, ataxia, dysarthria		1200	1.67		
Kores and Lader, 1997[11]	71/F	Cerebellar	Arrhythmia, tremor, dysarthria, ataxia			2.63	Trifluoperazine	Diuretic, NSAID
Kores and Lader, 1997[11]	64/F	Cerebellar, dementia	Diarrhea, muscle twitching, dementia, impairment of consciousness	NMS (fever not mentioned, but criterium of NMS)			Haloperidol	Diuretic, betablocker, diclofenac, coproxamol
Kores and Lader, 1997[11]	45/F	Cerebellar, mild dementia	Confusion, ataxia	Dehydration		3.6		
Kores and Lader, 1997[11]	42/F	Cerebellar, seizures	Agitation, seizures, spastic quadriplegia	Infection		2.18	Haloperidol	Erythromycin

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							Antipsychotics	Other Drugs
Meyer-Lindenberg and Krausnick, 1997[76]	72/F	Facial and abdominal dyskinesia (TD)	Ataxic gait, slurred speech, disorientation, blepharospasms, abdominal dyskinesia, chorea, intention tremor	Dehydration		1.1	No antipsychotics	
Epstein et al, 1997[21]	45/M	Cerebellar	Unconscious, seizures	Fever (heat stroke)	600		Haloperidol	Fluoxetine
Lal et al, 1997[20]	50/F	Cerebellar	Altered sensorium, general rigidity	Fever, NMS			Haloperidol	Amitriptyline
Normann et al, 1998[77]	62/M	Choreoathetosis	Severe delirium, EPS		900	0.8	Haloperidol	Amitriptyline, valproate
Brumm et al, 1998[78]	62/F	Dementia	Confusion, ataxia		Overdose (not specified)	3.9	Thiothixene	Benztropine
Bischof et al, 1999[79]	49/M	Cerebellar	Cerebellar syndrome	Fever (pneumonia)		0.7	Trifluperidol	Carbamazepine
Muthane et al, 2000[46]	65/F	Parkinsonism, facial dyskinesia (TD)	Akathisia, parkinsonism	Peripheral diabetic neuropathy, fever	900	1.5		
Van der Steenstraten en Achilles, 2001[19]	36/M	Cerebellar, cognitive deficits	Dysarthria, balance disorders, proximal muscle weakness, accommodation disorders	Fever (influenza)	1200	1.2	Pimozide	
Lang and Davis, 2002[80]	44/M	Cerebellar, plantar reflex	Dysarthria, ataxia, leg weakness, dyspnea		1200	1.5	Trifluoperazine	Amitriptyline, aspirin, felodipine, verapamil
Fabisiak et al, 2002[18]	21/F	Blindness (due to CPM, persisted for 4 months)	Extreme thirst, vomiting, diarrhea, facial paresis, blindness, wide-based gait		1050			
Bartha et al, 2002[17]	51/M	Cognitive deficits	Psychomotor slowing, dysarthria, incoherence		1350	2.4		
Tuglu et al, 2005[81]	62/F	Perioral dyskinesia (TD)	Lethargy, disorientation, upward gaze palsy, bradykinesia, cogwheel rigidity, rest and postural tremor		900	3.0	Olanzapine	
Ozsoy et al, 2006[82]	31/M	Cerebellar	Dysarthria, ataxia, dyskinesia, dysmetria, unable to walk or sit, intention tremor, bilateral horizontal nystagmus	Fever (pneumonia)	1200	0.9		Lamotrigine, escitalopram
Niethammer and Ford, 2007[83]	52/F	Cerebellar	Confused, ataxia, dysarthria			3.5		
Niethammer and Ford, 2007[83]	44/F	Cerebellar	Lethargy, nystagmus, ataxia	Fever (erythema multiforme)	1500	3.0	Perphenazine	Carbamazepine
Niethammer and Ford, 2007[83]	57/M	Cerebellar	Rigidity with bilateral jerking movements	Fever	600	1.98	Quetiapine	Paroxetine, valproic acid, propranolol

(*Continued*)

Table 1. Case Reports of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity in Published Peer Reviewed Literature (*Continued*)

Author and Publication Year	Age/ Gender	Nature of Persistent Sequelae	Acute Neurologic Signs	Precipitating Factors	Lithium Dose (mg/day)	Lithium Maximum Plasma Level (mM/L)	Co-Prescribed Drugs	
							Antipsychotics	Other Drugs
Tharoor et al, 2007[84]	28/M	Cerebellar	Generalized rigidity	Fever, NMS	800		Haloperidol, olanzapine	
De Cerqueria et al, 2008[16]	26/F	Cerebellar	Productive cough, vomiting, tremor, changes in gait, dysarthria, disorientation	Fever (pneumonia), dehydration	1500	1.9		
Keltner and Grant, 2008[15]	33/M	Severe neuropathy			2100 (accidental overdose)			
Fischera et al, 2009[85]	45/M	Cerebellar	Ataxia, dysarthria dysphagia	Pneumonia, hepatitis C, hemophilia B	1072	1.0		
Ikeda et al, 2009[86]	54/M	Cerebellar	Disorientation, tremor, dysarthria, hyperreflexia, coma	Fever	1200	3.45		
Porto et al, 2009[87]	44/F	Cerebellar	Altered mental status, severe disattention, disorientation, tremor, dysarthria		6000 (intentional overdose)		Haloperidol, chlorpromazine	
Kohen, 2011[88]	66/F	Cerebellar	Gait disturbance, confusion, dysarthria, ataxia, dysmetria, and dysphagia	Infection		2.0		
Van Landeghem en Vandenberghe, 2013[47]	61/F	Cerebellar	Confusion, dysarthria, nystagmus, recurrent falls, urinary incontinence, dysmetria	Dehydration, sensory neuropathy, alcohol abuse in past	750	1.2		Disulfiram, sertraline, trazodone
Feldman et al, 2015[89]	57/M	Cerebellar, EPS, brainstem dysfunction, cognitive impairment, perceptual disturbances	Altered mental status, perceptual disturbances, gait instability, tremors		900	2.6	Olanzapine	Tacrolimus, hydrochlorothiazide
Banwari et al, 2016[90]	35/M	Cerebellar	Vomiting, coarse tremor, ataxia, restlessness, dysarthria, dysmetria, dysdiadochokinesia, nystagmus		2000 (accidental overdose)	4.42	Olanzapine	
Banwari et al, 2016[90]	55/M	Cerebellar		Fever (upper respiratory tract infection)	900	2.52	Olanzapine	Clonazepam
Huang, 2016[91]	67/F	Cerebellar	Confusion, tremors, diarrhea	Fever	900	3.18	Quetiapine	
Cervello et al, 2017[92]	31/M	Cerebellar, basal ganglia micro lesions	Altered consciousness, tremor, agitation, rigidity, nystagmus		12000 (intentional overdose)	7.4	Aripiprazole	
Rossi et al, 2017[93]	33/M	Cerebellar		Fever (urinary tract infection)		1.18		
Medda et al, 2018[94]	68/F	Cerebellar	Tremor, bradykinesia, rigidity, postural instability	Fever	900	2.68	Pimozide	Carbamazepine, nortriptyline, imipramine, hydrochlorothiazide

(*Continued*)

Table 1. Case Reports of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity in Published Peer Reviewed Literature (*Continued*)

Author and Publication Year	Age/ Gender	Nature of Persistent Sequelae	Acute Neurologic Signs	Precipitating Factors	Lithium Dose (mg/day)	Lithium Maximum Plasma Level (mM/L)	Co-Prescribed Drugs	
							Antipsychotics	Other Drugs
Fountoulakis et al, 2019[95]	68/F	TD			600	0.6		
Cuigniez et al, 2020[96]	67/M	Cerebellar, TD, dementia	Confused, disorientation, agitation, word-finding difficulties, incoherence, coarse tremor		Accidental overdose	2.4	Quetiapine	Losartan, L-thyroxin, atorvastatin
Señga et al, 2020[97]	56/M	Encephalopathic illness	Altered mental status, seizures		900	2.8	Risperidone	Clonazepam, biperiden
Laranjinha et al, 2021[45]	54/F	Cerebellar	Slurred speech, agitation, seizures	Dehydration, mild mental retardation (?)	600	3.8		
Rhee and Kim, 2021[98]	46/M	Cerebellar, EPS	Delirium	Fever, NMS	Intentional overdose	1.63	Aripiprazole	Lorazepam
Jha et al, 2021[99]	50/M	Cerebellar	Dysarthria, past pointing, dysdiadochokinesis, wide-based gait		900		Risperidone	
Ocal et al, 2021[14]	59/F	Cerebellar, EPS	Speech impairment, lethargy, tremors, altered mental status	Fever, NMS	1200	2.16	Olanzapine	Levothyroxine
Akkus, 2022[100]	67/F	TD	Orofacial dyskinesia		1200	0.92		
Fenner et al, 2022[101]	49/F	Dementia	Confusion, short term memory deficits, myoclonus, chorea, ataxia			3.3		
Farouji et al, 2023[102]	61/M	Cerebellar, EPS	Confusion, disorientation, unsteady gait, agitation	Fever	Intentional overdose	>3.0	Quetiapine	Mirtazapine, gabapentin, doxepin, atorvastatin

CPM, central pontine myelinolysis; EPS, extrapyramidal symptoms; F, female; M, male; NMS, neuroleptic malignant syndrome; NSAID, nonsteroidal anti-inflammatory drug; TD, tardive dyskinesia.

sequelae, syndrome-based terminology was more common (e.g. cerebellar syndrome). Regarding acute signs, specificity regarding the nature of the symptoms was seldom provided; for instance, 'tremors' might encompass parkinsonian, cerebellar or other characteristics, but this distinction was not consistently specified. Consequently, we also recorded information in broad categorical terms.

The severity of the sequelae was not recorded, because there was also considerable variability in the reporting of this aspect. For example, for cerebellar sequelae, it ranged from moderate dysarthria to an advanced cerebellar syndrome rendering the patient dependent on assistance. Frequently, there was no further specification.

Acute Neurological Signs: The majority of cases (61.4%, n = 75) were characterized by an altered level of consciousness, ranging from confusion to comatose states, followed by dysarthria and/or ataxic gait (53.8%, n = 63) and 'tremors' (41.0%, n = 48).

Other typical acute neurological signs included pyramidal signs (hyperreflexia and/or plantar reflex and/or spasticity and/or myoclonus) in 17.9% (n = 21) of cases, bilateral nystagmus in 14.5% (n = 17), and seizures occurring in 9.4% (n = 11) of cases.

Persistent Sequelae: Cerebellar sequelae was mentioned in 77% (n = 90) of the cases, in 46% of the cases (n = 41) in combination with other sequelae. Cases without cerebellar sequelae accounted for 23% (n = 27).

Other commonly occurring sequelae included cognitive problems/dementia (19.7%, n = 23), parkinsonism/EPS (16.2%, n = 19), choreoathetosis (10.3%, n = 12), tardive dyskinesia (8.5%, n = 10), and peripheral neuropathy (6.0%, n = 7). Most of these sequelae were present in combination, but some also occurred as standalone sequelae (see Table 1 for an overview of these sequelae).

Risk Factors: In 47% of cases (n = 55), no precipitating factors were documented. In 41.9% of cases (n = 49), fever or infection, either concurrent or not, was reported. Dehydration was noted in 12% of cases (n = 14). Additionally, 4.3% of cases (n = 5) exhibited concurrent or past alcohol misuse, and a similar percentage, 4.3% (n = 5), experienced Neuroleptic Malignant Syndrome (NMS). The concomitant use of medications capable of elevating lithium levels, such as diuretics, NSAIDs, and certain antihypertensive drugs, was observed in 7.7% of cases (n = 9).

Therapeutic Approaches: We did not document the therapeutic approach employed following the development of SILENT, as such descriptions were infrequent and even less comprehensive. Invariably, therapeutic approaches predominantly consisted of general rehabilitation, encompassing physical therapy, speech therapy, and occupational therapy.

Discussion

This study conducted an analysis of 91 articles focusing on lithium toxicity and its associated neurological sequelae. Our review indicated that the most common clinical manifestations during the initial acute presentation involved an altered level of consciousness, followed by cerebellar signs. Similarly, the most frequently reported persistent sequelae also exhibited cerebellar characteristics. Fever and/or infection, followed by dehydration, were the most often reported risk factors. Applied therapeutic approaches were rarely mentioned and commonly involved a general rehabilitation of impaired functions.

Clinical Picture of SILENT

The onset of signs and symptoms related to lithium toxicity is gradual and insidious, which can lead to potential misinterpretation and misdiagnosis. Typically, it is only when the patient displays obvious and pronounced symptoms or when a clinical neurological examination reveals abnormalities that the possibility of lithium toxicity is taken into consideration.

The sequence of events often follows a rather typical pattern, resembling an acute organic brain syndrome (delirium), but frequently with gradually worsening symptoms, starting from early and relatively minor signs of intoxication to more severe manifestations. While this sequence of events is characteristic of acute lithium intoxication, a similar pattern is also observed, at least initially, in patients with long-lasting sequelae.

Cases of SILENT without an acute lithium poisoning phase are rare.[12] During the initial, acute toxic phase, various symptoms of an altered level of consciousness are commonly observed, such as altered mental state, confusion, disorientation, obtundation, lethargy, stupor or coma. Besides these symptoms, an acute cerebellar syndrome with symptoms such as wide-based ataxic gait, dysarthria, dysmetria, dysdiadochokinesia, hypotonia, nystagmus and (intention) tremor is also commonly observed in most cases.[9,103]

As the presentation of SILENT in most cases typically starts with an acute intoxication (acute or "acute on chronic"), in the initial phase, no conclusion can be drawn regarding the development of SILENT. In the meantime, one should promptly and effectively mitigate the toxicity as much as possible.[9,103]

Historically, cerebellar sequelae has been the most commonly neurological sequelae associated with SILENT, and we found a similar predominance in our study.

Risk Factors for Development of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity

Risk factors for developing an acute, "acute on chronic" or chronic lithium intoxication are well-known such as older age, reduced kidney function, dehydration, and concomitant use of diuretics.[2,104] Some of these factors were mentioned in the included cases like dehydration, concomitant use of diuretics or antihypertensive medications and fever/infection.

Individuals who use lithium long-term face an elevated risk for developing lithium-induced nephrogenic diabetes insipidus. This condition results in a loss of renal urine-concentrating ability, leading to an increased susceptibility to lithium intoxication.[104]

According to a recent systematic review, the connection between fever/infection and the development of cerebellar sequelae was observed primarily in cases with lithium plasma levels <2.5 mM/L independently from other characteristics. Furthermore, after adjusting for other variables, no correlation was observed between exposure to antipsychotics and the occurrence of cerebellar sequelae.[12] Nonetheless, one should be prudent to generalize the findings from

this review, as more large-scale studies are necessary to make firm conclusions.

It seems unlikely that the mechanism behind the temperature increase (fever or hyperthermia) plays a role, as the causal link between temperature elevation and cerebellar sequelae in lithium users is supported by the well-known sensitivity of the cerebellar cortex to temperature changes.[11,93]

Although lithium currently is mainly used in the treatment of bipolar disorder and (treatment-resistant) major depression,[4,105,106] it has been suggested that patients with schizoaffective disorder and marked psychotic symptoms may be more susceptible to lithium toxicity than most bipolar patients.[10,107]

Elderly patients also have a higher risk for lithium intoxication. It is estimated that approximately 25% of all patients with bipolar disorder are elderly,[108] who are deemed more vulnerable for various reasons. Recent and relatively preliminary research indicated that higher age is associated with an increased level of neurological soft signs (NSS), which are subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts. Moreover, bipolar disorder type I is associated with a higher degree of NSS compared to bipolar disorder type II. Furthermore, schizophrenia is linked to a greater extent of NSS than bipolar disorder.[109–111] It therefore could be hypothesized that elderly patients with one of these diagnoses might be even more susceptible to the potential (long-term) toxic effects of lithium.

Kidney function naturally decreases with age as part of the normal aging process. Generally, elderly patients also have a higher prevalence of comorbidities, such as cardiovascular diseases, impaired kidney function, and cognitive issues. Moreover, long-term lithium treatment is associated with an increased decline in GFR (glomerular filtration rate) and a doubled risk of developing chronic kidney failure.[112,113] As a logical consequence, older adults are at a higher risk of experiencing the adverse effects of lithium, including the development of (neuro)toxicity.[114] Therefore, lower lithium levels, that have been proven to be effective, are pursued.[106,115]

Higher lithium levels confer a higher risk of lithium toxicity. Even at lithium levels within normal limits, toxicity can occur. From clinical experience, we know that some people already develop toxic symptoms at lower levels, while others still do not show toxic symptoms at high levels.

The contributing factors are unknown. This requires high-quality and comprehensive research on this topic in a systematic and standardized way to better understand this phenomenon.

In none of the reports or reviews, we could find information on whether experiencing previous lithium intoxications makes individuals more susceptible to develop SILENT later in life if lithium therapy is continued.

Therapeutic Strategies

We presume that SILENT is frequently overlooked or attributed to other factors, especially in a population with chronic psychiatric conditions and defective features. It appears to encompass a spectrum of potential complications, with cerebellar sequelae being the most characteristic. Nonetheless, it is an extremely deleterious iatrogenic complication. The unpredictable nature of lithium neurotoxicity underscores the importance of vigilant patient monitoring and education. If symptoms of lithium intoxication arise, even with serum concentrations within the therapeutic range, it is crucial to reduce or discontinue lithium treatment until the symptoms subside. In some cases of elevated lithium levels, haemodialysis is started, though further refinement of the current EXTRIP criteria is necessary to offer more precise guidance on which lithium-intoxicated patients are likely to benefit from haemodialysis.[116] In fact, in clinical practice other levels of what is considered as toxic are used.[117] Moreover, there is currently insufficient evidence to suggest that this intervention can prevent the development of neurological damage.[118]

Once irreversible damage occurs, significant treatment challenges arise. While some patients recover spontaneously, even after two months, the extent of recovery varies. In certain cases, the sequelae persist despite the passage of time. The neurological sequelae should be treated according to available options. Physiotherapy focusing on enhancing balance reactions, trunk stability, and coordination, logopedic training for speech rehabilitation and addressing dysphagia-related concerns, and occupational therapy, to enhance overall self-sufficiency are utilized.[61,70]

A brief clinical neurological examination (including mental status, cranial nerves, motor and sensory assessment, coordination, reflexes and gait) to rule out subclinical signs of toxicity should undoubtedly be part of standard practice. Whether the implementation of NSS and cerebellar soft signs assessment in clinical practice provides added value will need to be determined through longitudinal studies that evaluate the associations between the severity of the pathology, psychosocial functioning, clinical outcomes, and structural and functional brain changes.[110]

Pathophysiology of Lithium-Induced Neurological Sequelae

Some neuropathological reports suggest that lithium may affect calcium homeostasis within Purkinje cells, leading to their selective impairment.[16,54,83] Adityanjee et al[9] proposed the hypothesis that lithium could induce demyelination in various brain regions, including the cerebellum. It has been reported that hyperthermia/fever can also cause cerebellar atrophy.[19,93] As described above, fever is linked with the development of cerebellar sequelae.[12]

Nevertheless, the exact mechanism behind lithium-induced neurological sequelae, with a seemingly propensity for selective cerebellar damage, remains unclear, and it is possible that it is not solely attributed to lithium-induced neurotoxicity. For instance, it could be linked to significant osmotic fluctuations caused by volume depletion and dehydration resulting from nephrogenic diabetes insipidus, which might be more prevalent among elderly individuals, chronic lithium users, and those with impaired kidney function.[116]

The Concept of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity

In accordance with other reviews[9–12] we used the definition of SILENT as introduced by Schou[7]: "prolonged neurological sequelae lasting for a minimum duration of two months after the discontinuation of lithium". Nevertheless, the validity of this definition remains a subject of debate. Tesio,[119] for example, proposed that the diagnosis of SILENT should involve the presence of persistent cerebellar signs for at least six months after the occurrence of lithium poisoning and

discontinuation of lithium treatment. Khanna[70] observed that significant continuous improvement can occur within the first 6 months, resulting in nearly complete recovery by the end of 9 months. In an effort to avoid therapeutic nihilism, it was therefore suggested by Khanna that the condition should be considered irreversible only if no substantial (less than 50%) recovery takes place in the initial 6 months. However, this proposal was not further explored or adopted. Taken all together, the concept of SILENT remains somewhat unclear.

As compared to previous reviews, the results of this scoping review did not reveal new findings about the syndrome, we can conclude that the scientific knowledge about this phenomenon has not advanced much since its initial reports. It is striking that, apart from available case reports and a few reviews, no dedicated research has been carried out to better understand this phenomenon. We also presume that there is significant underreporting of this syndrome due to a lack of recognition of cases that could potentially be diagnosed as SILENT. Although the use of lithium has become much more stringent than it has been in past years, and the occurrence of SILENT is rather exceptional, raising awareness about SILENT nevertheless remains crucial to avoid deleterious neurological consequences. This requires, in the first instance, a precise clinical description of the syndrome. Moreover, conducting high-quality and comprehensive research on this topic in a systematic and standardized way is also needed to better understand this phenomenon.

Limitations

Despite a comprehensive and systematic search of the literature, it is still possible that some relevant articles may have been missed as we excluded grey literature. We also excluded articles written in other languages than Dutch or English. Despite this, we believe that it is unlikely that these reports would have influenced the results significantly, due to the limited amount of cases they would add. Furthermore, there were great variations in the quality and depth of information provided in the included articles. The heterogeneity of reporting in case reports can pose challenges when attempting to synthesize the data.\

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