A reappraisal of the role of fever in the occurrence of neurological sequelae following lithium intoxication: a systematic review

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Abstract

Aim We aimed to review cases of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) characterized by neurological sequelae following acute lithium toxicity and to explore whether cerebellar sequelae are more frequent in cases presenting with fever and/or infection. Methods Case reports were identified from: (i) 6 reviews published up to 2005; (ii) MEDLINE, Web of Sciences, Cochrane Library and PsycINFO search. Results We identified 123 SILENT cases published from 1965 to 2019, in which cerebellar sequelae were observed in an overwhelming proportion (79%). Nearly two out of three cases (63%) had maximal lithium plasma level <2.5 mEq/l (low/mild toxicity). Fever and/or infection were reported in nearly half of the patients (48%). The likelihood of presenting with cerebellar vs. other neurological sequelae was independently increased by elevated plasma lithium level (? 2.5 mEq/l) (OR=4.36, 95%CI 1.31-14.52, p = 0.02) and by a history of fever and/or infection (OR=6.48, 95%CI 2.0-21.0, p = 0.002). Conclusions During the SARS-CoV-2 pandemic, prescribers have to be aware of the risks of cerebral sequelae associated with infection and fever in lithium users, and should warn them of the need to consult in case of fever to adjust their lithium dosage. As the occurrence of SILENT is exceptional, there is no need to modify lithium treatment preventively because of the pandemic as the benefit/risk balance of this drug remains largely positive.

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Lithium-induced neurological sequelae

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Methods Case reports were identified from: (i) 6 reviews published up to 2005; (ii) MEDLINE, Web of Sciences, Cochrane Library and PsycINFO search.

Results We identified 123 SILENT cases published from 1965 to 2019, in which cerebellar sequelae were observed in an overwhelming proportion (79%). Nearly two out of three cases (63%) had maximal lithium plasma level <2.5 mEq/l (low/mild toxicity). Fever and/or infection were reported in nearly half of the patients (48%). The likelihood of presenting with cerebellar vs. other neurological sequelae was independently increased by elevated plasma lithium level ([?] 2.5 mEq/l) (OR=4.36, 95%CI 1.31-14.52, p = 0.02) and by a history of fever and/or infection (OR=6.48, 95%CI 2.0-21.0, p = 0.002).

Conclusions During the SARS-CoV-2 pandemic, prescribers have to be aware of the risks of cerebral sequelae associated with infection and fever in lithium users, and should warn them of the need to consult in case of fever to adjust their lithium dosage. As the occurrence of SILENT is exceptional, there is no need to modify lithium treatment preventively because of the pandemic as the benefit/risk balance of this drug remains largely positive.

Key Words: lithium/ adverse drug reaction / neurotoxicity / fever / infection

1. Introduction

Lithium has well-established benefits regarding mood stabilization and prevention of suicide, which most often outweigh the risks associated with its use [1-3]. Intoxication is the most dreaded complication of lithium exposure since it is potentially life-threatening [4-7]. Exceptionally, lithium poisoning may be complicated by the occurrence of irreversible neurological sequelae. First described by Verbov in 1965 [8], this complication was defined by Schou in 1984 as the persistence of neurological sequelae more than two months after lithium discontinuation [9]. In 1987, Adityanjee proposed to name this complication SILENT (Syndrome of Irreversible Lithium-Effectuated NeuroToxicity) [10]. Although a wide range of persisting neurological syndromes have been reported, a consistent finding across the literature is the high proportion of cerebellar sequelae, especially ataxia and dysarthria [9, 11-15]. The occurrence of neurological sequelae in lithium users is a dramatic event as limited therapeutic resources are available (physical rehabilitation, speech therapy and cognitive training) [11, 13].

The most well-documented characteristic of SILENT is that it may occur in persons with plasma lithium levels within the therapeutic range, and at any time during lithium treatment [9, 11-15]. The potential neurotoxic impact of antipsychotic-lithium polytherapy has been widely cited in the literature on the risk factors of SILENT since the publication of four cases occurring in persons treated with haloperidol and lithium [16]. The possible role of fever and infections in the occurrence of cerebellar sequelae was first mentioned by Schou [9]. This hypothesis is supported by the high proportion of persons presenting with infections and/or fever among SILENT cases [9, 11-15].

Due to its narrow therapeutic index of lithium, prescribers' require updated accurate knowledge about the medical and lifestyle conditions increasing the risk of its adverse effects. At the onset of the SARS-CoV-2 pandemic, at a time when every psychiatrist around the world had to assess the benefit/risk ratio of psychotropic drugs in persons with COVID-19, we were struck by the fact that very few psychiatrists were aware that febrile infections might increase the risk of irreversible neurological sequelae in lithium users. Since our last review on this issue was undertaken nearly 30 years ago [15], we suspected that our knowledge about this complication might be outdated, motivating the current reappraisal of the literature. Of the five other reviews on SILENT cases [9, 11-14], the last one performed by Adityanjee included 90 cases published up to 2002 [11]. As antipsychotic prescribing practices have changed dramatically in lithium users since the introduction of second-generation antipsychotics [17], it is of interest to explore whether SILENT cases are still occurring. Furthermore, all prior reviews were exclusively narrative and did not explore which putative risk factors were independently associated with neurological outcome. Hence, the role of fever in the occurrence of cerebellar sequelae needs to be clarified.

The aim of the present study was to review published SILENT cases and to explore whether the occurrence of cerebellar neurological sequelae is more frequent in SILENT cases presenting with fever and/or infection, independently from other characteristics.

2. Methods

2.1. Identification of cases and search strategy

This review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. First, we considered the case reports identified in the six reviews published between 1983 and 2005 on neurological sequelae following lithium toxicity [9, 11-15]. Second, in order to identify new case reports not included in these prior reviews, we performed a MEDLINE, Web of Sciences, Cochrane Library and PsycINFO search from inception through July 2020 using the term "lithium" in combination with the following search terms (neurotox* OR neurologic* OR cerebel* OR SILENT). We examined related references of selected papers. Titles and abstracts of retrieved citations were screened, selected full-text articles were assessed independently for eligibility and data were extracted independently by two researchers. Disagreement was resolved by discussion.

We considered articles meeting the following inclusion criteria: (i) published in English, French, Spanish, Portuguese, Italian or German in peer-reviewed journals; (ii) reporting cases of neurological sequelae persisting more than two months after lithium discontinuation [9, 10]. We did not consider cases for which the observation period after lithium discontinuation was not specified or lasted less than two months, including cases with fatal outcome within the two-month period.

For each case, we extracted the following information: (i) reference: first author's name, journal, year of publication, (ii) demographic characteristics: age, gender; (iii) characteristics of lithium treatment: dose (mg/day), maximum plasma level (mEq/l); (iv) co-prescribed drugs: antipsychotics, other drugs; (v) associated medical conditions: fever, infection, dehydration, etc.; (vi) type of neurological sequelae: cerebellar (irrespective of presence of other sequelae) vs other (any other type of sequelae without associated cerebellar sequelae). Lithium maximum plasma level (mEq/l) was categorized according to the criteria proposed by the Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup [19]: i) no toxicity: <1.5 mEq/l); (ii) mild toxicity: [1.5-2.5[mEq/l; (iii) moderate toxicity: [2.5–3.5[mEq/l; (iv) severe toxicity: > 3.5 mEq/l.

2.2. Statistical analyses

Multivariate logistic regressions giving Odds Ratio and 95% confidence intervals (OR, 95% CI) were used to identify the characteristics independently associated with the type of neurological sequelae (cerebellar vs. other). Age was categorized as < 50 vs. [?] 50 ys. Lithium maximum plasma level (mEq/l) was dichotomized as "no/mild" (<2.5 mEq/l) vs. "moderate/severe" ([?] 2.5 mEq/l) toxicity. Antipsychotic exposure was categorized as present vs. absent irrespective of the number and type of antipsychotics. Exposure to fever

and/or infection was defined by the presence of at least one of the two conditions, irrespective of the cause of fever and the site of infection. Strictly defined fever included only cases with reported information on this symptom, irrespective of the cause. All the variables (age, gender, lithium level, antipsychotic use, fever) were simultaneously entered in the regression model. The models were not adjusted for lithium dose as this information was missing in a large proportion of cases.

3. Results

3.1. Results of literature search

Figure 1 presents a flow chart of the eligibility process for this review. One hundred cases published from 1965 to 2002 were identified in the 6 prior reviews [9, 11-15]. The numbers of additional cases fulfilling the inclusion criteria identified in each review are given in the flow chart. The systematic search identified 23 additional cases published from 1986 to 2019 [20-39].

Ultimately, we included 123 cases of neurological sequelae associated with lithium exposure reported in 92 articles published from 1965 to 2019 (Table 1). The number of reported cases peaked in the '80s. More than half of the 123 cases were published at the end of this decade, while very few cases have been published since the beginning of the 21st century (1960s: n=1; 1970s: n=21, 1980s: n= 48; 1990s: n=30; 2000s: n=15; 2010s: n=8). Most articles (n=75, 81%) reported a single case, and the maximal number of cases in an article was 7 [13].

3.2. Demographic characteristics

There were 53% (n=65) females and 47% (n=58) males. The mean age of cases was 46.8 (standard deviation 13.3, range 20-70), with 57 cases (46.3%) aged [?] 50 years.

3.3. Lithium treatment

The median daily prescribed dose of lithium was 1200 mg (interquartile range 900-1500). Twelve (9.8%) overdoses were reported (intentional n=8, accidental n=3; not specified n=1).

Using the EXTRIP classification, the distribution of maximum lithium level was: (i) no toxicity <1.5 mEq/l n= 42 (38.5%); (ii) mild toxicity [1.5-2.5[mEq/l n=27 (24.8%); (iii) moderate toxicity [2.5–3.5[mEq/l n=20 (18.4%); (iv) severe toxicity > 3.5 mEq/l n=20 (18.4%). A plasma level > 5 mEq/L indicating the need for extracorporeal treatments (ECTRs) [19] was reported in 7 (6.4%) of patients. Information on lithium level was missing in 24 cases.

3.4. Co-prescribed drugs

Antipsychotics use was reported in half of the cases (n=61, 49.6%). First-generation antipsychotics were used in most cases (n=58, 95.1%), the most frequently reported being haloperidol (n=30), chlorpromazine (n=16), thioridazine (n=4) and fluphenazine (n=4). Four patients used second-generation antipsychotics (olanzapine n=3 and quetiapine n=1).

Other reported psychotropic and non-psychotropic treatments are detailed in Table 1. The most frequently reported were antidepressants (n=14), anticonvulsants (n=10) and benzodiazepines (n=8).

3.5. Associated medical conditions

Fever and/or infection was reported in nearly half of the patients (n=59, 48%). Information on the presence of fever was absent in 9 patients with infection. The most frequent infection was pneumonia (n=12) [25, 29, 34, 40-45]. Probable or definite neuroleptic malignant syndrome was observed in 6 patients [22, 28, 35, 36, 46, 47], and heat stroke in one patient [23]. The other medical conditions (anorexia, surgery, dehydration, chronic kidney disease, alcohol use, etc.) are described in Table 1.

3.6. Type of neurological sequelae

Cerebellar sequelae were reported in most cases (n=97, 78.9%) and were the only neurological syndrome in 58 cases (60.4% of those with cerebellar symptoms). The other frequently reported neurological sequelae were cognitive deficits/dementia (n=17, 13.8%), choreoathetosis (n=12, 9.8%), parkinsonism (n=11, 8.9%), dyskinesia (n=9, 7.3%) and peripheral neuropathy (n=7, 5.7%). Other rare sequelae are described in Table 1.

3.7. Characteristics associated with occurrence of cerebellar sequelae

Multivariate analyses were performed in the sample of cases without missing data on the variables of interest (n=109, 88.6%). Two characteristics were independently associated with the occurrence of cerebellar sequelae (Table 2): plasma lithium level [?] 2.5 mEq/l (moderate/severe toxicity) and (ii) presence of fever and/or infection. An association was found at trend level between age and type of sequelae, the proportion of patients aged 50 years and over being higher in the group with cerebellar sequelae. No association was found between type of sequelae and gender or antipsychotic use.

To further explore whether the impact of fever on the occurrence of cerebellar sequelae was modified by lithium plasma level, the interaction term "fever*lithium level" was entered in the multivariate model. As this interaction was significant (Wald test Chi2=6.31, p=0.01), we performed analyses stratified by maximum lithium plasma levels. This showed that the association between fever and/or infection and cerebellar sequelae was strong (OR=13.9, 95%CI 3.21-60.05) in cases with no/ mild lithium toxicity, while it was not significant in those with moderate/severe lithium toxicity (OR=0.92; 95%CI 0.12-7.10).

Sensitivity analyses using the variable "strictly defined fever" (i.e. cases with reported information on this symptom) showed comparable associations between fever and cerebellar sequelae: 40 (47.1%) patients with cerebellar sequelae had a history of fever vs. 4 (16.7%) of patients with other sequelae (OR=5.65, 95%CI 1.65-19.37, p=0.006).

4. Discussion

4.1. Main findings

We identified 123 cases of neurological sequelae associated with lithium exposure published from 1965 to 2019, including 23 additional cases not identified in prior reviews. Cerebellar sequelae were observed in an overwhelming proportion of cases (79%). Nearly two out of three cases (63%) had a maximal lithium plasma level <2.5 mEq/l indicative of low/mild toxicity [19]. Fever and/or infection were reported in nearly half of the patients (48%). The likelihood of presenting with cerebellar vs. other neurological sequelae was independently increased by elevated plasma lithium level ([?] 2.5 mEq/l) and by a history of fever and/or infection. Stratified analyses showed that the association between fever/infection and occurrence of cerebellar sequelae was restricted to cases with lithium plasma level <2.5 mEq/l.

4.2. Interpretation of findings

While the incidence of SILENT in the population of lithium users is unknown, this complication may be considered as exceptional considering that the 123 cases identified in the present review were published over a 55-year period. The decreasing frequency of published cases after the '90s may be explained by a lower publishing rate of new cases, as is often the case when a drug adverse effect is considered as already well-documented in the literature. This decrease might also be related to changes in prescribing practice over the last decades, with a wider use of anticonvulsants and second-generation antipsychotics in bipolar disorder, leading to low rates of lithium exposure in the general population [17, 48, 49]. Due to the severity of this complication, it is important to keep in mind that SILENT cases are still occurring despite these changes in prescribing practices.

The clinical characteristics of the SILENT cases identified in the present review are comparable to those reported in prior reviews [9, 11-15]. These severe complications of lithium treatment are most frequently observed during routine lithium treatment, with fewer than 10% of cases occurring after accidental or intentional overdoses. Consistently with this low rate of overdose, plasma lithium levels were within the

therapeutic range in a large proportion of cases. In cases with toxic plasma lithium levels, several factors known to increase plasma levels were noted such as anorexia [8], dehydration [50], chronic kidney disease [51] or coprescription of diuretics [13, 38, 52, 53].

Typically, the inaugural clinical picture is an episode of acute lithium poisoning with little symptomatic specificity. Neurological symptoms are frequently observed during these episodes, such as tremor, rigidity, hyperreflexia, myoclonia, disorientation, drowsiness or seizures, and transient cerebellar symptoms (dysarthria, ataxia, nystagmus) may also be present [6, 13]. Cases of SILENT without an acute lithium poisoning phase are rare [54].

The questions raised since the observation of the first cases of SILENT are why these neurological symptoms exceptionally persist after the resolution of the acute episode, and why cerebellar sequelae are so frequent in SILENT cases. The neurotoxicity of antipsychotic-lithium polytherapy in general and of haloperidol-lithium was long considered as a plausible hypothesis explaining the occurrence of these cases [12, 16] and is still mentioned as a key factor in the recent literature on drug-induced cerebellar syndromes [37, 55]. However, the existence of a causal link between exposure to haloperidol and the occurrence of SILENT was soon questioned as the frequency of haloperidol-lithium polytherapy was comparable in persons with and without neurological sequelae [9, 56]. In the present review, half of the cases were prescribed antipsychotics, a prescription pattern comparable to that observed in persons with bipolar disorders treated in the last decades of the 20^{th} century [57]. No association was found between exposure to antipsychotics and the occurrence of cerebellar sequalae after adjusting for the other variables.

The striking elevated frequency of cases of SILENT with a history of fever or infection, first noticed by Schou [9], is confirmed in the present study. What the latter adds to prior narrative reviews is to show that fever is associated with an increased risk of cerebellar sequelae, independently from other characteristics, and that this increased risk is restricted to cases with plasma lithium levels <2.5 mEq/l (no/mild toxicity)[19]. In the group with no/mild toxicity, more than two thirds (71%) of patients with cerebellar sequelae had a history of fever/infection vs. 17% of patients with other sequelae. Conversely, the presence of fever/infection was not associated with the type of neurological sequelae in the group of cases with lithium levels [?] 2.5 mEq/l (moderate/severe toxicity).

These findings suggest that two distinct pathophysiological pathways may lead to neurological sequelae induced by lithium. This hypothesis is speculative and has to be regarded as an oversimplification of the complex relationships between cerebellar sensitivity to both lithium neurotoxicity and fever. Schematically, the first pathway is characterized by an episode of lithium poisoning with elevated lithium levels leading to a wide range of neurological sequelae, including cerebellar ones, perhaps because the lithium neurotoxic threshold is reached everywhere in the nervous system. The second pathway is marked by the occurrence of cerebellar sequelae after a febrile intercurrent episode in patients with lithium levels within the therapeutic range or moderately elevated, perhaps because the lithium neurotoxic threshold is lower in this brain area in the event of fever. The biological plausibility of a causal link between fever and risk of cerebellar sequelae in lithium users is supported by the long-known sensitivity of the cerebellar cortex to heat and hyperthermia [13, 37]. The most consistent neuroanatomical findings found by brain imaging and post-mortem studies are cerebellar atrophy and loss of Purkinje cells [43, 46, 54, 58-62].

4.3. Implications for clinical practice

Decades after the event, prescribers who have encountered such cases keep a vivid memory of patients confined to a wheelchair [9, 46]. As therapeutic resources are limited, prevention of SILENT is crucial and requires prescribers' awareness about the following points, which synthesize the key findings with implications for clinical practice drawn from current and prior reviews [9, 11-15]:

1. SILENT may occur at any time during lithium treatment, from a few days after treatment to decades after.
2. SILENT may occur even when lithium plasma levels are within the therapeutic range. Hence, the clinical symptoms of neurotoxicity are more important than the lithium level for deciding modifications

of lithium treatment.

3. Fever dramatically increases the risk of cerebral sequelae. The literature demonstrates that all causes of fever (infection, neuroleptic malignant syndrome, heat stroke, etc.) appear to be associated with this increased risk, and it is possible that no minimal hyperthermia can be considered as safe [27].
4. Based upon the literature and the present findings, we recommend the interruption of lithium or at least a dose reduction in the event of fever. As no guidelines are currently available regarding this point, it might be recommended to halve the dosage of lithium. Even if there is a risk of mood recurrence due to lithium withdrawal [63, 64], this risk may be considered as low when the treatment is interrupted only over a few days, and it is negligible compared to the risk of neurological sequelae. Hence, the strategy recommended for lithium in the event of fever or infection should be very close to that recommended for clozapine, the other psychotropic drug with a narrow therapeutic index [65-68].
5. When lithium users benefit from therapeutic education about the symptoms of neurotoxicity and conditions promoting the occurrence of these symptoms (dehydration, coprescription of diuretics or NSAID, etc), they should receive special warning about the fact that fever, irrespective of its cause, may induce lithium toxicity and that they must consult in the event of fever in order to adapt their dosage.

It is beyond the scope of the present paper to review the management of lithium poisoning: the cornerstones are the early identification of neurotoxic symptoms and the use of aggressive lithium removal methods [5, 6, 19, 69]. Owing to the low incidence of SILENT, no study has examined which strategy may help to prevent neurological sequelae. However, neurological symptoms are known to persist more frequently at intensive care unit discharge in patients with lithium poisoning not treated by extracorporeal toxin removal [6].

4.5. Limitations

The present review is limited by the fact that data were extracted from published case reports who may not be representative of all cases of neurological sequelae occurring in persons exposed to lithium. For instance, we cannot exclude that a publication bias may exist for cases presenting with cerebellar symptoms, leading to an overrepresentation of such cases in the literature. However, such a bias, if any, should not have impacted the direction and strength of the association between fever and occurrence of cerebellar sequelae, as a systematic publication bias of cases with fever and cerebellar symptoms is unlikely. Furthermore, we may have missed some published cases, but we have little reason to suspect that we selectively missed cases presenting with features different than those identified in the present review. Lastly, a third unknown factor and therefore not adjusted for in the present analysis, and independently associated with increased risk of fever and increased risk of cerebellar sequelae, may confound this association.

4.6. Conclusion

During the SARS-CoV-2 pandemic, prescribers have to be aware of the risks of cerebral sequelae associated with infection and fever in lithium users, and should warn them of the need to consult in the event of fever to adjust their lithium dosage. As the occurrence of SILENT is exceptional, there is no need to preventively modify lithium treatment because of the pandemic as its benefit/risk balance remains largely positive, including with respect to neuroprotection [70, 71].

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Competing interest

There are no competing interests to declare

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Data availability

Not relevant

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