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Lithium nephrotoxicity: when and why? Experience of nephrology and psychiatry outpatient clinics

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Abstract

Background: Lithium salts are widely used in the treatment of bipolar disorders. Lithium–induced nephropathy is a complication occurring after several years of lithium exposure and accounts for 0.2% of the dialysis population. Whether other pre-existing renal pathologies may potentiate or accelerate this progression of lithium nephropathy is a controversial matter. Therefore, the aim of this case-controlled study was to analyse and identify the factors which may influence long-term renal outcome.

Methods: The clinical and laboratory data of 7 patients of the nephrology unit who were under long-term lithium therapy and had moderately to severely impaired renal function (G3a-G5), were compared to that of 7 psychiatry clinic patients under the same treatment whose renal function was normal or mildly compromised (G1-2). The lithium nephropathy diagnosis was based on the presence of long-term lithium treatment, renal impairment and/or the presence of renal cysts. The population characteristics, including comorbidities, duration of lithium treatment and its dosage and episodes of toxicity were taken into account.

Results: The patients in the G3a-G5 group had more pre-existing renal conditions and had a higher incidence of severe nephropathy despite being treated for a shorter amount of time and with lower lithium doses compared to the patients in the G1-2 group. Moreover, they presented additional risk factors such as lithium intoxication and nephrogenic diabetes insipidus.

Conclusion: Careful assessment of pre-existing renal disease should be performed before initiation of lithium therapy, especially in elderly co-morbid patients with multiple risk factors. Close monitoring and patients' education are mandatory for patients who undergo long-term lithium treatment.

Introduction

Lithium salts have been sparsely used in psychiatry since the mid-19th century. The discovery of their efficacy in the treatment of mania is credited to John Cade, an Australian psychiatrist, who observed their clinical effectiveness in 1949 [1]. Nowadays, lithium has been demonstrated to be effective in the treatment of acute mania and bipolar depression, as well as in the prophylactic treatment of bipolar disorder, and as an augmentation agent in the treatment of unipolar major depression. Lithium is also the only mood stabilizer that has been demonstrated to lower the suicide rate in patients with bipolar disorder [2]. Despite all these applications, its mechanism of action is still unknown.

It is recognized that chronic kidney disease (CKD) is a serious adverse effect of long-term lithium therapy that usually occurs after 10-20 years or more of administration [3]. However, the data concerning lithium-induced end stage renal disease (ESRD) is limited. In a large-scale epidemiological study, the prevalence of CKD was found to be about 1.2%, comparable to the general population [4]. It has been reported that when chronic renal failure occurs, its progression is slow (loss of 2.29 mL/min/year in terms of glomerular filtration rate) and its evolution into ESRD is rare, with an incidence of Lithium-induced ESRD ranging from 0.2% to 0.7% [5,6].

However, others have found that lithium related chronic ESRD accounts for 0.22% of all ESRD cases [7]. From a pathological point of view, lithium-induced nephropathy is characterized by a chronic tubulo-interstitial disease. Other features, such as focal segmental glomerulosclerosis (FSGS) and/or renal microcysts may also be present. As far as the pathophysiology is concerned, lithium accumulates in the distal tubule and the collector duct via the epithelial sodium channel (ENaC), inhibiting glycogen synthase kinase 3 beta (GSK3b) and activating b-catenin. These phenomena interfere with the pathways which are crucial for the proliferation of the tubular cell [7].

Various factors have been postulated as potential risk factors for the progression of lithium nephropathy.

The aim of this this observational case control study is to identify possible factors and/or pre-existent conditions which might influence the rate of decline of the GFR in patients, with or without impaired renal function, receiving lithium treatment.

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Materials and methods

In this case control study, we compared two groups of patients under chronic lithium therapy. We reviewed the clinical and laboratory data of 7 patients suffering from lithium nephropathy and under lithium salts treatment who attended a nephrology outpatient clinic. Their data were compared with that of 7 patients of a psychiatry unit who were under lithium treatment and had no apparent diagnosis of lithium nephropathy. In the first group (G3a-G5) the patients had a moderately or more severely reduced renal function (eGFR < 60 ml/min/1.73m^2, MDRD), whereas in the second group (G1-2) they had a normal or mildly impaired renal function (eGFR ≥ 60 ml/min/1.73m^2, MDRD).

The lithium nephropathy diagnosis was based on the presence of long-term lithium treatment, renal impairment and/or the presence of renal cysts. The population characteristics, including comorbidities, duration of lithium treatment and its dosage and episodes of toxicity were taken into account.

Results

Overall, we identified 14 Caucasian patients treated with lithium (7 male and 7 female). As shown in Table 1, in the G3a-G5 group there were 5 men (71.43%) and 2 women (28.57%). Mean age was 71 + 10. The mean duration of lithium therapy was 251.57 + 130.04 months and lithium posology were 481.43 + 217.29 mg. Six patients (85.71%) had serum lithium levels >= 0.6 mmol/l. As far as in the G1-2 group is concerned, there were 2 men (28.57%) and 5 women (71.43%). Mean age was 63 + 7 years. The mean duration of lithium therapy was 294.86 + 50.84 months and lithium posology were 685.

No statistically significant age differences were detected (t-test, t12 = 1.20, P = 0.25).

With regard to pre-existing conditions, in the G3a-G5 group 5 patients (71.43%) had a nephropathy, 5 had nephrogenic diabetes insipidus (71.43%), 5 had hypertension (71.43%), 3 had abdominal adiposity (42.86%), 2 had cardiac insufficiency (28.57%), 1 had hepatic dysfunction (14.29%), 2 had a history of NSAIDs use (28.57%).

By contrast, pre-existing renal conditions in the G1-2 group were encountered in only one patient (14.29%), who had nephroangiosclerosis due to chronic hypertension (Table 2).

With respect to risk factors related to lithium nephropathy progression, in the G3a-G5 group there were 3 patients (42.86%) who experienced episodes of acute lithium intoxication and 5 developed nephrogenic diabetes insipidus (71.43%). In the G1-2 group no patients presented lithium-related side-effects, such as acute lithium intoxication and/or nephrogenic diabetes insipidus (Table 3).

Discussion

This small study, in which patients with moderate to severe lithium nephropathy were compared with matched patients who had no or mild nephropathy, shows that a pre-existing renal disease may increase the chances of patients progressing into ESRD.

In fact, as displayed in Table 2, 5 patients in the G3a-G5 group exhibited pre-existing renal conditions, whereas none in the G1-2 group did. Nephroangiosclerosis secondary to chronic hypertension was the most common renal disease encountered in the G3a-G5 group. Though chronic hypertension is well-known to be a major risk factor for the development of nephroangiosclerosis, its influence on lithium-related nephropathy has not been extensively investigated. Nevertheless, the fact that CRF is not always reversed after discontinuation of lithium therapy [8] could be explained by the presence of an unknown pre-existing renal condition such as nephroangiosclerosis. This condition, due to chronic hypertension, has a long-term slow progression [9] and may therefore be mistaken for the effects of lithium on the kidneys. The hypothesis of pre-existing nephroangiosclerosis is also supported by the concomitant finding of hypertensive cardiomyopathy in 2 patients in the same group (Table 2).

On the other hand, Markowitz et al. [8] postulated that people with a more advanced CRF had more chances of progressing to an ESRD after lithium treatment discontinuation, probably because of progressing renal fibrosis [10].

Table 1. Patients characteristics

Characteristic	All Patients (N=14)	G3a-G5 group (N=7)	G1-2 group (N=7)
Male sex – no (%)	7 (50%)	5 (71.43%)	2 (28.57%)
Female sex – no (%)	7 (50%)	2 (28.57%)	5 (71.43%)
Mean age - yr	67 ± 9	71 ± 10	63 ± 7
Mean duration of lithium therapy - months	273.21 ± 97.48	251.57 ± 130.04	294.86 ± 50.84
Median duration of lithium therapy - months	300	228	300
Mean Lithium posology - mg	583.57 ± 195.71	481.43 ± 217.29	685.71 ± 106.9
Median Lithium posology - mg	600	450	600
Serum lithium levels => 0.6 mmol/l) – no (%)	11 (78.57%)	6 (85.71%)	5 (71.43%)

Table 2. Patients co-morbidities and risk factors

Pre-existing conditions	All Patients (N=14)	G3a-G5 group (N=7)	G1-2 group (N=7)
Nephropathy – no (%)	5 (35.71%)	5 (71.43%)	0
- Nephroangiosclerosis		- 4 (57.14%)	0
- Interstitial Nephritis		- 1 (14.29%)	0
Hypertension alone – no (%)	2 (14.29%)	1 (14.29%)	1 (14.29%)
Diabetes – no (%)	0	0	0
Cardiopathy – no (%)	2 (14.29%)	2 (28.57%)	0
Hepatopathy – no (%)	1 (7.14%)	1 (14.29%)	0
NSAIDs use – no (%)*	2 (14.29%)	2 (28.57%)	0

*One patient developed interstitial nephritis (included in the nephropathy group)

Table 3. Lithium-related risk factors

Risk factors	All Patients (N=14)	G3a-G5 group (N=7)	G1-2 group (N=7)
Acute lithium intoxication – no (%)	3 (21.43%)	3 (42.86%)	0
Nephrogenic diabetes insipidus – no (%)	5 (35.71%)	5 (71.43%)	0

The relevance of pre-existing renal conditions may also be supported by the fact that the G3a-G5 group presented a higher incidence of severe nephropathy, despite being treated for a shorter amount of time and with lower lithium doses compared to the patients in the G1-2 group (Table 1).

These data differ from the evidence of some other studies. Bendz et al. identified a clear correlation between the duration of lithium treatment and the decline of the GFR [4] and Davis et al. also insisted on the importance of the duration of treatment, whereas the relevance of the daily dose of lithium (1 versus 2 times a day) is still disputed [11].

Age and concomitant use of nephrotoxic medications are well documented risk factors. Additionally, a lower eGFR value before the start of treatment, predicts an accelerated progression of the nephropathy, especially among women [11]. Surprisingly, the patients in the G3a-G5 group were mostly men. However, this inconsistency is likely to be justified by the small size of the groups.

Moreover, the group of patients with severe nephropathy presented additional risk factors such as lithium intoxication and nephrogenic diabetes insipidus, which are known to accelerate the progression of ESRD. Nephrogenic diabetes insipidus may be a surrogate marker for early morphological changes occurring within the kidney tubules which predict the development of lithium associated nephropathy [11].

Furthermore, Davis et al. [11] also identified nephrogenic diabetes insipidus as a possible risk factor since volume contraction leads to elevated lithium concentrations and, in turn, to lithium toxicity. As pointed out by Shine et al. in their retrospective study [12], episodes of lithium intoxication seem in fact to play a crucial role.

In our G3a-G5 group, 3 patients (42.86%) had episodes of acute lithium intoxication and 5 patients (71.43%) had nephrogenic diabetes insipidus, while none of the patients in the G1-2 group presented these risks factors (Table 3).

The main limitation of the present study is indeed its size. Further studies with larger patient pools and regular assessments of renal function are needed. However, given the fact that the negative effects of lithium therapy take several years to show, and that lithium is a treatment for the underdiagnosed bipolar disorder [13], this might prove difficult.

We can conclude that special attention must be paid, and a closer follow-up should be organized when introducing lithium therapy in older co-morbid patients with multiple risk factors and an abnormal renal function. It is therefore of crucial importance to obtain eGFR at the start of therapy, and to screen the patient in order to detect a possible pre-existing renal disease. In addition, close follow-up of risk factors such as the monitoring of serum lithium levels and of diabetes insipidus development is mandatory. These measures are crucial for avoiding episodes of lithium intoxication, which are extremely detrimental in terms of the decline of renal function, and should be combined with patients' education, as proposed by Le Roy et al. [14].

The American Psychiatric Association recommends screening for nephrotoxicity in patients on lithium therapy by measuring the serum creatinine level every 2-3 months during the first 6 months of lithium therapy and every year thereafter [15]. However, further elements are needed in order to better stratify the risk of developing chronic renal failure, such as episodes of dehydration-related lithium intoxication.

Conclusion

Long-term treatment with lithium salts may favour the development of ESRD and accelerate the course of an underlying nephropathy. Careful assessments of potential underlying renal disease should be performed before initiation of lithium therapy, especially in elderly co-morbid patients with multiple risk factors. Close monitoring and patients' education, as well as interdisciplinary follow-up by psychiatrists and nephrologists are mandatory for patients undergoing long-term lithium treatment. Larger studies are required to understand the implication of pre-existing renal disease on the progression of lithium nephropathy.

Declarations

Ethics approval and consent to participate: All patients received a letter of information and consequently had the opportunity to express their disagreement with the use of the health data. Approval from the local ethical committee: Comitato etico cantonale, which is the regional committee for Canton Ticino of Swissethics (Swiss Association of Research Ethics Committees). Project-ID 2020-02055, Rif CE TI 3733.

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