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Research paper

Cardiovascular comorbidity increases the risk for renal failure during prophylactic lithium treatment

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ABSTRACT

Background: The development of lithium-associated kidney damage is still a matter of controversy. We have addressed this question by investigating the role of somatic comorbidity for developing kidney failure in lithium treated patients.

Methods: The study group comprised of 1741 adult patients with normal creatinine levels at the start of lithium treatment. Patients who developed severe renal failure (CKD stages 4–5, $n = 109$), were matched by sex, time on lithium and age at start of lithium, with 109 controls (CKD stages 1–2) that did not develop severe renal failure.

Results: Patients in CKD 4–5 did not differ significantly from controls (CKD 1–2) in sex (females/males were 76/33 in both groups), time on lithium (mean 9.8 years, SD 6.4; vs. 9.6, SD 6.2) or age at start of lithium (mean 61.6 years, SD 13.4; vs. 60.5 years, SD 12.3), respectively. However, comparisons between groups showed a significantly higher prevalence of somatic comorbidity ($p < 0.001$), especially cardiovascular diseases ($p < 0.003$), among patients in CKD 4–5.

Limitations: Patients in our study group were relatively old and the findings are therefore not generalizable to patients starting lithium at an early age. The retrospective design, relying on available charts, did not allow to grade severity of comorbid conditions other than need for hospitalisation or chronic drug treatment.

Conclusions: Our findings emphasize the role of somatic comorbidity for renal damage in lithium treated patients and especially the role of cardiovascular comorbidity. Monitoring of somatic comorbidity should be taken into account in treatment recommendations and safety routines in long-term prophylactic lithium treatment.

1. Introduction

Lithium enjoys the strongest evidence among today´s mood stabilisers for long-term relapse prevention of bipolar disorders and has been shown to reduce the risk of suicide. However, the benefits of lithium are restricted by its adverse side effects, the most serious being the progression of renal insufficiency to end-stage renal disease (ESRD) with need for renal replacement therapy (RRT, i.e. dialysis and renal transplantation).

We have previously shown that the prevalence of RRT in the lithium user population in Sweden was 1.5% and the relative risk for RRT in the lithium user population compared to the general population was 7.8 (Aiff et al., 2014). This can be compared with a study by Close et al. (2014) that showed a hazard ratio of 2.5 for renal failure in lithium treated subjects. These findings suggest that ESRD is an uncommon but not rare complication of lithium treatment. There are also population based studies that do not show a significant effect on kidney function with lithium compared to controls (Clos et al., 2015). However, in a cohort of 630 patients on lithium for 10 years or more we found that serum creatinine had increased by >30% in 45% of the patients and about 10% had developed serious renal insufficiency with ensuing risk of ESRD (Aiff et al., 2015). A previous study by Kessing et al. (2015), has shown an increased risk of chronic kidney disease (CKD) in patients with bipolar disorder per se, unrelated to drug treatment. Time on lithium seem to be a risk factor for lithium nephropathy (Bocchetta et al., 2015). Therefore, the clinically important question still remains, namely when to stop lithium therapy to prevent progressive impairment of kidney function which may result in ESRD. Furthermore, the results from our previous studies indicate that the development of renal insufficiency during lithium treatment cannot be explained by lithium exposure alone but that additional factors are operative.

Our hypothesis is that somatic comorbidity plays a crucial role for

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the development of lithium-associated kidney damage. The primary aim of the present study was to investigate the impact of comorbid somatic disorders on the progression of severe kidney damage during lithium treatment and subsequently to promote clinical care by increasing patient safety.

2. Patients and methods

2.1. Patients

We conducted a retrospective longitudinal study, including patients with at least one positive lithium measurement between 1 January 1981 and 31 December 2010, using the database at the Department of Clinical Chemistry at Sahlgrenska University Hospital in Sweden. The database was established in the 1970s and includes laboratory data from all laboratories serving the public hospitals and out-patient clinics in the greater Gothenburg area with a population of approximately 650.000 inhabitants. We retrieved the serum lithium and creatinine levels together with age and gender of all patients examined during this 30-year period.

Patients who had a positive lithium measurement in 1980 were not included, as we aimed to recruit patients who started their treatment during the 'modern' lithium era in accordance with today's treatment routines with S-lithium adjusted individually and kept as low as possible with standardized S-lithium measurement within 0.5–0.8 mmol/L, in addition to regular and frequent monitoring of renal function. A total of 4879 patients had their lithium concentration measured during the study period.

Patients with less than one year on lithium treatment were excluded together with patients younger than 18 years as they probably had therapeutic rather than prophylactic lithium treatment. Patients without creatinine measurements might have had their follow-up elsewhere and were excluded due to missing data. We also excluded patients with an initial creatinine level above the laboratory reference value (adjusted for age and gender), to avoid patients with disease processes already affecting the kidneys at the start of the lithium treatment. If a patient had 365 days without any positive lithium measurements, this was regarded as a discontinuance of lithium treatment and that time period was subtracted from the total treatment duration.

To follow up patients in the study group after the end of inclusion in 2010 we retrieved serum creatinine concentrations from 2011 through 2013 from the database. The serum creatinine measurement closest (± 6 months) to the first lithium measurement was regarded as the initial creatinine level. Patients without initial creatinine measurements within this period were excluded. The last available serum creatinine measurement until the end of 2013 was regarded as the final creatinine concentration. The study cohort then consisted of 1741 adult patients with at least 1 year of lithium treatment and normal serum creatinine levels at the start of lithium treatment (Fig. 1).

The glomerular filtration rate was estimated (eGFR) from the serum creatinine concentration, age and gender according to the Revised Lund-Malmö formula devised by Björk et al. (2011). The eGFR based on the final creatinine level was used to categorize the achieved level of renal function in 5 stages of chronic kidney disease (CKD) according to the KDOQI guidelines (Nkf, 2002).

Based on the final eGFR measurement, 1241 patients were classified as having CKD stage 1–2 (eGFR ≥ 60 ml/min), 404 patients CKD stage 3 (eGFR < 60ml/min but ≥30 ml/min), while 109 patients reached CKD stage 4–5 (eGFR < 30ml/min).

2.2. Methods

To study the impact of somatic comorbidity we initiated a matched case-control study of patients in CKD stage 4–5 (cases, n = 109) compared with 109 matched controls in CKD stage 1–2 (controls, n = 109).

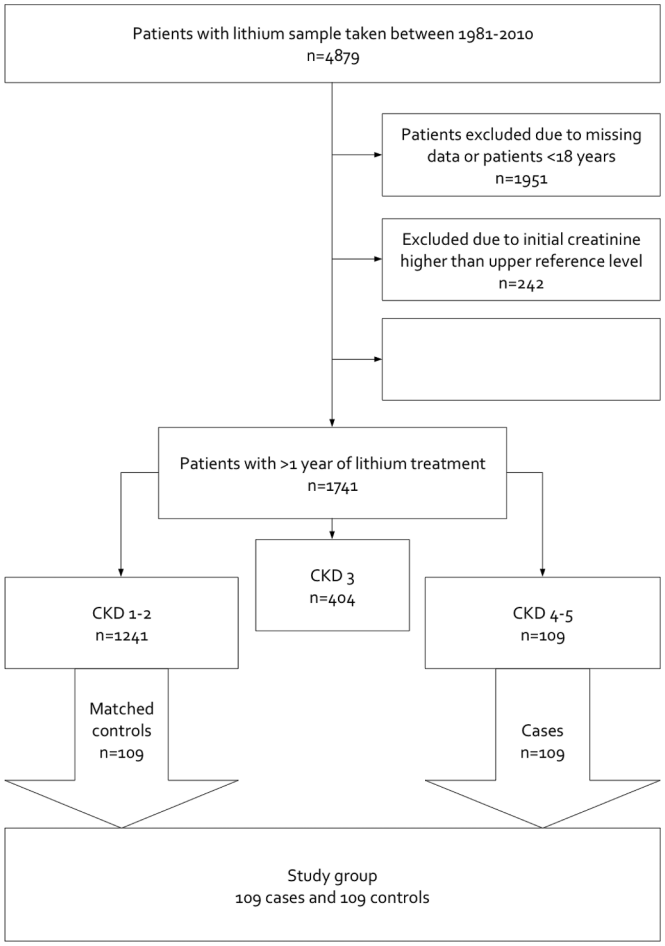

Fig. 1. Selection of study patients.

Cases and controls were matched by sex, time on lithium (± 2.5 years) and age at start of lithium. The presence or absence of severely reduced kidney function was used as the dependent variable and all medical diagnoses recorded through chart reviews as independent explanatory/predictive variables. Furthermore, to assess the extent of comorbidity or global burden of somatic disease we added the number of comorbid diseases to a total score per patient.

2.3. Chart reviews

Assessment of somatic comorbidity was based on structured reviews of individual medical charts including death certificates by 2 of 3 physicians. The reliability of our chart ratings was enhanced by specified criteria for classification of medical diagnoses indicating chronic somatic diseases and by inter-rater consensus of all not clear-cut decisions.

To classify the somatic comorbidity we defined the presence of chronic disease as diseases that needed hospital treatment or chronic medication, in each disease category. We then selected from the comorbid spectrum of the patients those conditions that are recognised as related to progression of renal damage and functional insufficiency. These include cardiovascular disease, diabetes mellitus, malignancy, urological conditions and pre- or coexisting renal disease.

In the present study cardiovascular disease is a composite characterisation of fatal and non-fatal myocardial infarction, angina pectoris, cardiac arrhythmias, heart failure, cerebrovascular and peripheral vascular disease and hypertension. Diabetes mellitus includes both insulin-dependent and non-insulin dependent disease. Urological conditions include obstructive conditions and congenital aberrations of the