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Original Article

Monitoring of glomerular filtration rate in lithium-treated outpatients—an ambulatory laboratory database surveillance

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Abstract

Background. The long-term risk of chronic kidney disease (CKD) in lithium (Li)-treated patients has been well established in the recent years.

Methods. We have evaluated GFR and serum calcium monitoring in 1179 Li-treated outpatients from an ambulatory laboratory database study. This has been performed in a single private laboratory in Paris from February 1997 to December 2004. Estimated GFR (eGFR) has been calculated using the abbreviated MDRD equation.

Results. During an 8-year period, 695 patients (59%) had at least one serum creatinine measurement, whereas 484 had no creatinine measurement. The former group had also more frequent serum Li measurements. Mean serum lithium levels, were similar in both groups, 0.65 mmol/l *vs* 0.62 mmol/l. The percentage of patients with CKD stage 3 (eGFR 30–59 ml/min/1.73 m^2) were 36%, 53%, 73% and 77%, and with CKD stage 4, 3%, 5%, 5%, 8% in patients aged 20–39, 40–59, 60–69, and $\geq$70 years respectively. There was no significant rise in creatinine measurements (from 35% of the patients with at least one serum creatinine in 2003 to 39% in 2004; $P = 0.66$) despite intervention to intensify GFR monitoring by physicians. Serum calcium was tested at least once in 212 patients (18%) of whom 15 (7%) were found with hypercalcaemia.

Conclusion. A very high percentage of Li-treated outpatients have low eGFR. GFR monitoring is neglected in these patients, the majority of whom are no longer attending specialized clinics. Hypercalcaemia is less common but serum calcium monitoring is even more neglected. Ambulatory laboratory database surveillance provides a powerful means to contribute to CKD screening and monitoring.

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Introduction

The long-term risk of chronic kidney disease (CKD) in lithium (Li)-treated patients is well documented from clinical, histopathological [1–3], and epidemiological studies [3–5]. This complication occurs mostly in patients receiving Li for >10–20 years. In addition, hypercalcaemia due to hyperparathyroidism is recognized as a complication of Li administration [3,4]. Most studies, however, have been performed from cohorts of patients followed-up in psychiatry hospitals or nephrology clinics. In contrast, no information is available on the glomerular filtration rate (GFR) and serum calcium monitoring in community-based Li-treated patients. As it has been recently underlined by Garg *et al.* [6], ambulatory laboratory database screening is of great importance to identify subjects with low GFRs, to obtain information on GFR monitoring in well-defined segments of population and to design and evaluate intervention strategies to improve screening in populations at high risk of CKD.

Such an approach has, therefore, been used in the present study to evaluate the monitoring of renal function and serum calcium among Li-treated outpatients and to estimate the prevalence of reduced GFR. Information to intensify GFR monitoring was also sent to the physicians in charge of these patients and the impact of this intervention was evaluated.

Patients and methods

This study was performed in a single private ambulatory laboratory where serum Li levels of many treated outpatients living in Paris were measured. We conducted a retrospective

longitudinal study using this laboratory database including all patients with at least one Li measurement between February 1997 and December 2004. Overall, 1179 Li-treated patients (733 females, 446 males) were tested during this 8-year period. Seventy-seven percent received lithium carbonate, 13% slow-release Li carbonate and 10% received either treatment. A total of 9464 serum Li, 2027 serum creatinine and 374 serum calcium measurements were available. In December 2003 and February 2004, a letter was sent to all prescribing physicians with information about the need for annual GFR and serum creatinine and calcium measurements as recommended for Li-treated patients.

Serum Li, creatinine and calcium concentrations were measured with standard methods. The creatinine assay, a modified kinetic Jaffe colorimetric method, was retrospectively calibrated to the Cleveland Clinic Foundation Clinical Laboratory (Jaffe CX3 Beckman) as described previously [7]. In a few words, spiked samples obtained by addition of increasing amounts of creatinine hydrochloride (Sigma Chemicals) to normal plasma were tested in parallel in the private laboratory in which data of the study were obtained and in an academic clinical research laboratory previously calibrated to the CCF assay. This led to corrected creatinine values that were then used for the calculation of estimated GFR (eGFR). GFR was estimated using the abbreviated MDRD equation [8], assuming that all patients were Caucasians, and was expressed in ml/min/1.73 m^2 body surface area. KDIGO recommendations were used to stratify GFR groups [9]. Low GFR was defined as <60 ml/min/1.73 m^2.

Mean (*m*) and standard deviation (SD) are presented unless otherwise specified. Student's *t*-test and χ^2 test were used to compare personal and treatment data between patients with at least one creatinine measurement and those without any. To evaluate the impact of information to the physicians, the percentages of patients with at least one creatinine measurement before and after the intervention were compared.

Results

Among the 1179 Li-treated patients, only 695 (59%) had at least one serum creatinine measurement during the study period. The median age of the overall cohort at baseline was 56 ± 15 years and 62% of the patients were women. Patients with at least one serum creatinine measurement did not significantly differ from those without any with respect to age, gender and baseline serum Li levels, but they had significantly more serum Li measurements, and were more likely to receive slow-release Li carbonate (Table 1).

The distribution of eGFR classes according to age group at first creatinine measurement is shown in Table 2. The percentages of patients with eGFR <60 ml/min/1.73 m^2 were 39%, 58%, 78% and 85% in patients aged 20–39, 40–59, 60–69 and ≥70 years, respectively. These percentages were clearly higher than those found in the Fourth National Health and Nutrition Examination Survey (NHANES IV) [10] or in the Hunt II study [11], carried out in US and Norwegian adults, respectively (Figure 1). On the other hand, 3–8% of the patients (Table 2) had CKD stage IV (eGFR 15–29 ml/min/1.73 m^2).

The prevalence of low eGFR increased with age (Figure 1), but was very high, 39%, in the youngest age group (20–39 years). Mean serum Li levels, however, were not significantly higher in this group than in the older age groups (data not shown). The percentage of patients with serum creatinine measurements was

Table 1. Description of the study cohort

	Subjects with at least one creatinine measure	Subjects without creatinine measure	*P*
N	695	484	
Women (%)	64%	59%	NS
Mean age at baseline (years)	57 ± 14	56 ± 16	NS
Type of Li treatment over the study period			
Li carbonate	72%	85%	
Slow-release Li carbonate	14%	11%	< 0.0001
Li-carbonate or slow-release Li carbonate	15%	4%	
Mean value of serum Li at baseline (mmol/l)	0.66 ± 0.22	0.62 ± 0.25	NS
Total number of Li measurement: median (range)	8[4; 16]	2[1; 4]	<0.0001

Table 2. Distribution of GFR categories by age group at the first creatinine measurement

eGFR categories *vs* age classes	*N*	15–29	30–59	60–89	≥90
20–39	91	3%	36%	53%	8%
40–59	294	5%	53%	39%	2%
60–69	170	5%	73%	22%	0%
≥70	140	8%	77%	15%	0%

eGFR is expressed in ml/min/1.73 m^2.

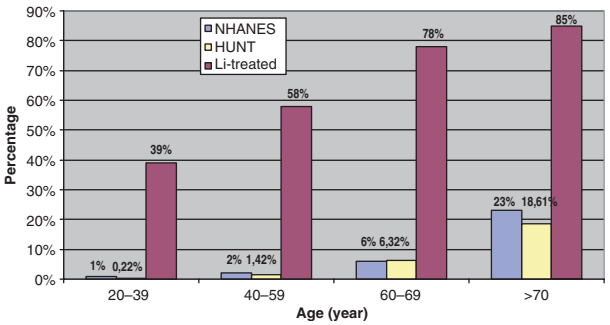

Fig. 1. Percentage of Li-treated patients with eGFR <60 ml/min/1.73 m^2 as compared with NHANES IV and Hunt II studies [10,11].

rather similar in the various age groups: 52%, 61%, 63% and 55% in 20–39, 40–59, 60–69 and ≥70 years groups, respectively. Three hundred eighty-five patients had at least two creatinine measurements, 290 of whom had these two measures at least 1 year apart. In the latter, the median GFR decline was 0.57 ml/min/1.73 m^2/year (25% quartile, −4,13; 75% quartile, +2.83 ml/min/1.73 m^2/year). Of these 290 patients, 44% had initial eGFR <60. No significant change in eGFR emerged in these 290 subjects with repeated eGFR measurements. The median interval between measurements was 42 months, ranging from 12 to 94.

Monitoring of GFR

Between 1997 and 2003, the percentage of patients with at least one creatinine measurement increased from 25% to 35%. After two letters of information sent to the physicians in charge of the patients, this percentage did not rise significantly, 35% to 39% in 2004 ($P = 0.66$).

Serum calcium measurements

Serum calcium was measured at least once in 212 patients (18%). Fifteen of them (7%; mean age 65 ± 10 year) had a serum calcium level >2.625 mmol/l (10.5 mg/dl). During the study period, 17% of the patients had at least one measurement of plasma TSH level.

Discussion

Our study highlights the interest of an ambulatory laboratory database surveillance focused on a selected population, i.e. lithium-treated patients identified by regular serum Li measurements. The prevalence of low eGFR (<60 ml/min/1.73 m^2) is much higher in this population than in the general population, whatever the age groups.

The reference populations were US adults from the fourth National Health and Nutrition Examination Survey (NHANES IV) and Norwegian adults from the HUNT II study [10,11]. No comparable data were available in the French population except in the elderly where the estimated prevalence of low eGFR was 29% in participants ≥70 from the French '3 Cités' study [12], Although creatinine measures in our cohort as well as in Hunt II and the 3 Cities studies were calibrated to the CCF assay used in NHANES IV, comparing prevalences of low GFR based on estimated rather than measured GFR remains a limitation of this study, as there was no information on body composition of the patients.

Our results confirm previous data originating from nephrology clinics and indicating that renal failure, including ESRD, is not unusual in patients chronically treated with Li for long periods of time (>10–20 years) [3,4]. In our survey, among 695 outpatients tested, 261 had eGFR between 30 and 59, and 24 had stage 4 chronic kidney disease (eGFR: 15–29 ml/min/1.73 m^2). In a recent study from a Psychiatry Division, Lepkifker *et al.* [5], found that 21% of 114 patients treated with Li for a mean period of 16.75 years had a serum creatinine concentration ≥133 μmol/l on two consecutive measurements. However, such a threshold underestimates the prevalence of renal functional impairment.

The prevalence of low GFR increased with age. It has been shown in several studies that overall duration of Li therapy was longer in patients with renal impairment than in others [3,5]. Of note, 39% of the patients aged 20–39 had low eGFR, including two of them with eGFR between 15–29 ml/min/1.73 m^2. Li therapy however may be initiated early in life: the mean age ± SD at initiation was 43.17 ± 12.05 years, and the youngest patient at initiation of Li was 15 years of age in the study by Lepkifker *et al.* [5]. In addition renal insufficiency may develop early in some rare patients. In the abovementioned study [5], the mean duration of Li therapy was 16.5 years in patients with renal insufficiency. However, five of them developed renal failure within 10 years after initiation of Li therapy. Similar observations had been made in previous studies [2,3]. No clear progression of renal impairment could be documented in our study because the rate of progression of lithium-induced nephropathy is usually very slow [3].

This study enabled us to assess the quality of GFR monitoring in Li-treated outpatients. This monitoring is far from being optimal in usual medical care conditions in the Paris area. Patients treated with slow-release preparation, however, had tighter monitoring of Li (and consequently of creatinine) than those treated with other types of preparation. It is usually recommended to have an annual determination of serum creatinine in these patients. The percentage of patients tested increased slightly from 35% to 39% after information directed to prescribing physicians. More prolonged efforts are necessary to increase awareness of Li renal toxicity among patients and physicians, and to implement regular measurements of serum creatinine. Similarly, more attention should be paid to Li-induced hypercalcemia [3,4].

Finally, studies performed from an ambulatory laboratory database have limitations. In the present study, no information was available on the duration of Li treatment, blood pressure level, potentially associated renal disease, independent of Li toxicity. Detailed medical analysis could not be performed. In contrast, this approach may be of great interest to identify easily segments of the population with persistent reductions in GFR, more specifically segments of the population who are at high risk of developing CKD. As stated repeatedly [3,5], the majority of lithium-induced patients are no longer attending specialised clinics and are at risk to develop CKD insidiously unless eGFR is regularly monitored.

The lifetime incidence for bipolar disorder, the main indication of chronic lithium therapy, is about 1%. Despite recent advances, lithium is still the 'quintessential mood stabilizer' in this disease [13]. Psychiatrists, general practitioners and nephrologists should coordinate their efforts to screen renal function in outpatients chronically treated with Li. Ambulatory laboratory database surveillance provides a powerful mean to contribute to this screening.

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