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Lithium-induced nephropathy: Rate of progression and prognostic factors

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Lithium-induced nephropathy: Rate of progression and prognostic factors.

Background. Long-term lithium administration in humans may lead to chronic tubulointerstitial nephritis, which develops very slowly. Its progression to end-stage renal disease (ESRD) has been rarely reported. The aim of this study is to document the rate of progression of lithium-induced nephropathy and its prognostic factors, and to provide an estimation of the percentage of lithium-induced ESRD in France.

Methods. Two groups have been studied: 54 patients with lithium-induced renal failure, nine of whom underwent renal biopsy; and 20 patients who were referred for systematic renal biopsy, 14 of whom were subsequently followed up. In addition, a survey of lithium-induced ESRD was conducted in French dialysis centers.

Results. The mean annual loss of creatinine clearance in patients with lithium-induced nephropathy was 2.29 mL/min. Among 74 patients, 12 reached ESRD at a mean age of 65 years. Creatinine clearance at referral and at last follow-up was inversely related to the duration of lithium therapy in both univariate and multivariate analyses adjusting for age, gender, hypertension, and proteinuria. The degree of interstitial fibrosis on renal biopsy was also related to the lithium duration and cumulative dose. It was predictive of the final creatinine clearance. About 35% of the patients tested had moderate hypercalcemia, due to hyperparathyroidism. The prevalence of lithium-related ESRD in France was estimated as two per 1000 dialysis patients. The average latency between onset of lithium therapy and ESRD was 20 years.

Conclusion. Lithium-induced chronic renal disease is slowly progressive. Its rate of progression is related to the duration of lithium administration. Lithium-related ESRD represents 0.22% of all causes of ESRD in France. Regular monitoring of estimated creatinine clearance is mandatory in long-term lithium-treated patients.

Key words: chronic renal failure, nephrotoxicity, hypercalcemia, hyperparathyroidism, adverse lithium effects.

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Chronic administration of lithium salts has been used from 1949 for the prophylaxis of recurrences in uni- or bipolar affective disorders (see review in [1]). Its efficacy was quickly recognized and it has been widely used by psychiatrists since the early seventies. In the middle 1970s, it was estimated that about one in 1000 individuals in Western countries received lithium therapy [2].

Lithium nephrotoxicity was first documented at the end of the nineteenth century but this problem was more extensively investigated in recent decades with the more widespread use of this drug. Impaired renal concentrating ability is found in approximately 50% of the patients, and polyuria and polydipsia (due to nephrogenic diabetes insipidus) occur in about 20% of the patients chronically treated with lithium [3]. Of interest, this side effect may persist despite cessation of the treatment, pointing to irreversible renal damage [4]. The possible development of lithium-induced chronic tubulointerstitial nephritis was first demonstrated in 1977 by Hestbech et al [5] in 14 patients treated with lithium for about 2 to 15 years, five of whom had acute lithium intoxication [5]. Subsequently renal damage induced by long-term lithium treatment in susceptible patients was documented [6, 7]. Markowitz et al [8] recently reemphasized the risk of often irreversible biopsy-proven lithium toxicity, responsible for combined glomerular and tubulointerstitial damage.

The question of lithium-induced chronic renal failure (CRF) has long been debated from the conflicting results of cross-sectional and longitudinal epidemiologic studies (see review in [9]). Some of these studies have stressed how renal insufficiency was infrequent and mild in lithium-treated patients. Others have underlined the effects of confounding factors on renal function, such as aging, concomitant and chronic administration of other psychotropic or nonpsychotropic medications, and perhaps the psychiatric disease itself [2]. From the data collected

in 14 studies, including 1172 patients, Boton, Gaviria and Batlle [3] estimated that the prevalence of reduced glomerular filtration rate (GFR), measured by different methods, was 15%.

The aim of the present study is to analyze the rate of progression of renal failure in a group of patients with lithium-associated chronic nephritis and to correlate the progression rate with the duration of lithium therapy and with the severity of the renal histopathologic changes. In addition, preliminary epidemiologic data on lithium-induced end-stage renal disease (ESRD) have been collected to draw attention to this emerging cause of ESRD, which may increase progressively with time, paralleling the increasing duration of lithium administration.

METHODS

Patients

Seventy-four patients on lithium therapy were included in this study from 1970 to 2001. Fifty-four of them were referred for CRF to two Paris hospitals (Hôpital Necker and Hôpital Bichat-Claude Bernard). Chronic lithium administration was the only cause of renal disease. During the same period, six patients on chronic lithium therapy were seen but excluded from this study because they had evidence of another cause of renal disease: bilateral partial nephrectomy for cancer (one patient), idiopathic retroperitoneal fibrosis (one patient), ureterohydronephrosis (two patients), reflux nephropathy (one patient), and vasculitis (one patient). The other 20 patients participated, after informed consent, in a systematic evaluation of lithium nephrotoxicity. These patients were followed up at Hôpital Ste Anne, treated with lithium for at least 5 years, and then referred to Necker hospital in 1980 for renal biopsy. Fourteen of these 20 patients had subsequent follow-up and their renal status was reevaluated at last examination. Six have been lost to renal follow-up.

For each serum creatinine measurement, creatinine clearance was estimated according to the Cockcroft and Gault formula [10]. For each patient and each period, with or without lithium, a regression curve was determined and used to calculate creatinine clearance variation in mL/min/year.

Data on proteinuria, leucocyturia, hematuria, lithium dosage, and serum calcium concentration were collected. Proteinuria was considered as significant when above 300 mg/24 hours. Microhematuria was defined as $\geq$10,000 erythrocytes/mL of urine. Patients were considered as hypertensive when blood pressure was $\geq$140/90 mm Hg or when they were receiving antihypertensive therapy. The therapeutic range of serum lithium concentration was 0.5 to 0.8 mmol/L. Acute lithium intoxication was defined as serum lithium concentration above 1.5 mmol/L with central nervous system abnormalities, acute renal failure, and electrocardiographic changes. Hypercalcemia was defined as a serum calcium concentration above 2.6 mmol/L. Polyuria was defined as more than 3 L per 24 hours.

Finally, a survey was performed among the French dialysis centers. Questionnaires were sent to all nephrologists in charge of the 242 dialysis centers in France to obtain information on the dialysis patients with lithium-induced nephropathy. No national registry is available in France.

Renal pathology

Twenty-nine patients underwent a renal biopsy, 20 belonging to the cohort studied in 1980, and nine to the group of patients referred for CRF. Renal biopsies were studied by light microscopy with standard methods. Paraffin sections were stained with silver (Jones method), periodic acid-Schiff, hematoxylin and eosin, Masson's trichrome, and were examined by the same pathologist (L.H.N.). The following items were graded according to a scale of 0 (absent) to 3 (severe): interstitial fibrosis and tubular atrophy, interstitial inflammation, arteriosclerosis and arteriolosclerosis. Interstitial fibrosis was graded semiquantitatively according to the criteria of Banff classification used for kidney transplants [11]. The percentage of sclerotic glomeruli was recorded. Tubular cysts and dilatations were defined as tubules with a diameter of at least 5 times and 2 to 4 times that of normal tubules, respectively.

Statistical analysis

Continuous variables are reported as mean $\pm$ SD.

We analyzed the relation between daily lithium dose, duration of treatment, serum lithium concentration and three outcome variables: baseline creatinine clearance, creatinine clearance at the end of follow-up, and decline in creatinine clearance. The decline in creatinine clearance was also studied continuously in two categories (below or above 2 mL/min/year), whereas the two other outcome variables were studied continuously. Chi-square test, analysis of variance and correlation coefficient were used to study crude relations between lithium exposure and the outcome variables. Multiple regression analysis and logistic regression were used to adjust for (*1*) age and gender; (*2*) age, gender, and hypertension; and (*3*) age, gender, and proteinuria. Subsidiary analysis of the relations between exposure variables and both calcemia and fibrosis was performed, but these relations were not adjusted because of the small number of subjects.

RESULTS

Patients' characteristics

They are described in Table 1. The female/male gender ratio is 1.55. The patients have been treated with lithium

Table 1. Main clinical characteristics of the lithium-treated patients

	All patients (1)	Patients who progressed to ESRD (2)	Other patients (3)	*P* value (2) vs. (3)
Number of patients	74	12	62	
Gender *F*/*M*	46/28	6/6	40/22	NS[a]
Age at the onset of lithium *year*	42.9 ± 10.5	39.9 ± 12.8	43.5 ± 9.9	NS
Duration of the lithium therapy *year*	19.8 ± 8	21.7 ± 6.2	19.4 ± 8.3	NS
Total dose *g*	5231 ± 2554	5041 ± 2762	5260 ± 2524	NS
Serum lithium concentration *mmol*/*L*				
Mean	0.62 ± 0.05	0.62 ± 0.08	0.67 ± 0.11	NS
Maximal	0.91 ± 0.28	0.91 ± 0.28	1.02 ± 0.49	NS
Creatinine clearance at the beginning of follow-up *mL*/*min*	62.6 ± 29.5	39.1 ± 23.3	67.1 ± 28.6	0.002
Last creatinine clearance *mL*/*min*	41.4 ± 27	7.2 ± 2.1	48.1 ± 24.4	<0.0001
Loss of creatinine clearance *mL*/*min*/*year*	−2.29 ± 2.64	−4.1 ± 2.2	−1.92 ± 4.02	NS
Number of hypertensive patients	38	8	30	NS[a]
Follow-up *years*	10 ± 7.8	8.9 ± 5.5	10.2 ± 8.1	NS
Number of patients who interrupted lithium therapy				
Temporarily	8	3	5	NS[a]
Definitively	17	3	14	

Mean ± SD; Student *t* test.
[a]Chi-square test

since a mean age of 42.9 years, for unipolar (14 patients), bipolar (57 patients), and schizophrenic-affective disorders (3 patients). The estimated cumulative dose of lithium salt (mostly lithium carbonate) could be calculated from the medical records of only 66 patients. Fourteen patients were treated with lithium only, 60 had additional psychotropic drugs (antidepressants, neuroleptics, or benzodiazepines). Hypertension was present in 38 patients whereas only 25 received antihypertensive therapy, including an angiotensin-converting enzyme (ACE) inhibitor in three patients and an angiotensin II type 1 (AT-1) receptor blocker in three others. The mean number of medications was 1.65. Nine patients were given thyroid substitution because of hypothyroidism. Two patients had regularly taken nonsteroidal anti-inflammatory drugs or analgesics that did not contain phenacetin, respectively.

Lithium therapy

Mean lithium therapy duration was 19.8 years corresponding to an estimated cumulative lithium salt of 5231 g per patient (Table 1). At least one serum lithium concentration was known in 54 patients. The frequency of lithium measurements was once a month in 21 patients and about three to four determinations per year in the others. Mean serum lithium concentration was 0.62 mmol/L. Twenty-one patients had a serum lithium concentration above 1 mmol/L at least once. Four patients had acute lithium intoxication. In two patients this occurred in the first months after dialysis initiation.

Renal abnormalities

Polyuria and polydipsia were present in 25 patients among 54 (46%). Sixty two patients were examined for proteinuria and only 11 showed significant proteinuria (mean, 1.29 g/24 hours; range, 0.35 to 4.1). Six patients had proteinuria above 1 g/24 hours. Five of these proteinuric patients had a renal biopsy. Thirteen patients out of 55 (24%) had microscopic hematuria, 10 of these patients had a renal biopsy, and 16 out of 52 (31%) had leucocyturia. At the beginning of the follow-up, mean creatinine clearance was 62.6 mL/min and dropped to 41.4 mL/min at the end of the follow-up, after a mean period of 10 ± 7.8 years (range, 3 months to 32 years). Renal function loss, estimated in 70 patients followed up for more than 1 year and calculated from creatinine clearance, was 2.29 ± 2.64 mL/min/year (Table 1 and Fig. 1). Two patients who had lithium therapy in two different periods of their lives are reported twice in this figure.

Twelve patients reached ESRD at a mean age of 65 years (range, 46 to 85 years). They had begun the treatment at the same age as the other patients, had taken the same amount of lithium over a slightly longer period of time (Table 1). In five of these 12 patients, multiple serum lithium concentrations were available and did not differ from those of the other patients. At entry in the study, these patients had a more impaired renal function than the others and their mean annual loss of creatinine clearance was slightly higher ($P = 0.08$). Among the nine patients who progressed to ESRD and in whom proteinuria was looked for, six had a significant proteinuria, whereas among the other 52 patients, only four had proteinuria ($P < 0.0001$).

Relation between lithium therapy and renal functional impairment

Patients who received lithium for 20 years or more had lower creatinine clearance at entry into the study

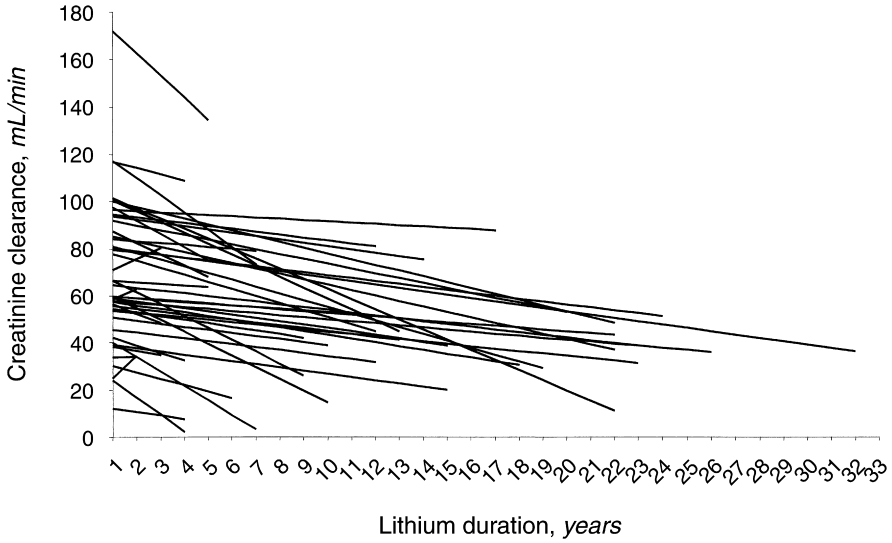

Fig. 1. Evolution of estimated creatinine clearance over time in 35 patients on lithium therapy. Each line denotes the evolution in one patient followed up for more than 1 year.

Table 2. Relations between lithium daily dose, treatment duration, and progression of renal function

Lithium salt administration	Creatinine clearance				Decline of creatinine clearance			
	At entry into the study		At the end of follow-up		Mean annual decline		Decline >2 mL/min/year	
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	%	OR[a] (95% CI)
Daily dose								
<750 mg	25	46 ± 18	24	34 ± 17	24	−1.65 ± 5.50	25.0	1
≥750 mg	41	73 ± 31	41	48 ± 30	39	−2.51 ± 2.70	51.3	3.0 (1.0–9.3)
P[b]		<0.001		0.06		0.45		
Duration								
<20 years	29	72 ± 36	29	53 ± 34	27	−2.53 ± 5.71	44.4	1
≥20 years	43	56 ± 22	42	32 ± 17	42	−2.07 ± 1.96	45.2	0.9 (0.3–2.6)
P[b]		0.020		<0.001		0.59		

[a] Odds ratios adjusted for age and gender (95% confidence interval)
[b] *P* value of the comparison between groups from the multiple regression analysis, including age and gender as covariates

and at the end of follow-up than the others (Table 2). The patients who received a daily dose above 750 mg/day had a slightly but not significantly greater annual loss of creatinine clearance. However, patients who received more than 750 mg/day were three times more likely to experience an annual creatinine clearance decline above 2 mL/min than those who recieved a lower dose. These relations were not explained by age and gender (Table 2) and remained unchanged after adjusting for either hypertension or proteinuria (data not shown).

Estimated creatinine clearance inversely correlated with the length of lithium therapy (Fig. 2) and more weakly with the mean serum lithium concentration. However, it did not correlate with maximal serum lithium concentration or lithium daily dose. This is probably explained by reverse causation (i.e., the progressive decrease in lithium dose as far as renal function declined).

The treatment was stopped in 25 patients, temporarily in eight (lithium had to be reintroduced to control the psychiatric disease) and definitively in 17 other patients. Eleven patients were followed up for more than 1 year before and after their treatment interruption. There was a slight reduction in the rate of progression of CRF after the lithium treatment interruption ($P = 0.067$). Of interest, six of the 12 dialysis patients had interruption of lithium therapy. Despite definitive discontinuation, three patients progressed to ESRD in 2 to 13 years. Their estimated creatinine clearance at interruption ranged from 15 to 27 mL/min. Lithium therapy had to be reintroduced during regular dialysis period in two patients. When creatinine clearance was above 40 mL/min at lithium discontinuation, renal function improved in five of seven patients with a mean increase in creatinine clearance of 1.57 mL/min/year; whereas it continued to deteriorate in 12 of 18 patients at a mean rate of −2.64 mL/min/year when creatinine clearance was ≤40 mL/min at cessation. Furthermore, when lithium was interrupted below 25 mL/min all patients continued to deteriorate.

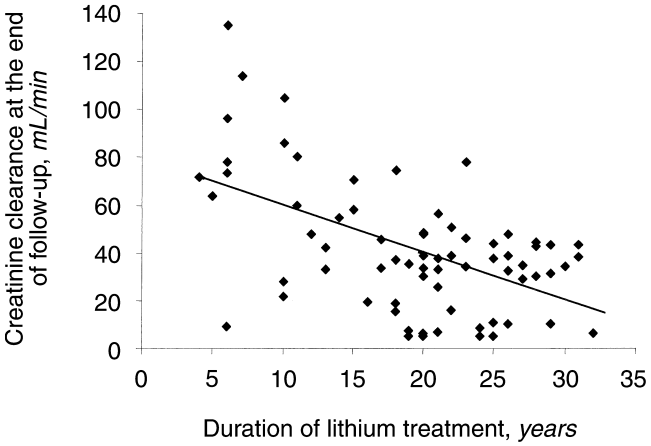

Fig. 2. Correlation between creatinine clearance at the end of follow-up and lithium treatment duration. (◆) Each patient.

Calcium disorders

A concentration of serum calcium was determined in 46 patients. Its mean was 2.52 ± 0.23 mmol/L. Sixteen patients (35.6%) had hypercalcemia ranging from 2.60 to 3.0. Parathyroid hormone (PTH) level was measured in only nine hypercalcemic patients. The mean PTH level was 96.4 pg/mL (range, 48 to 180; normal, 10 to 65). Six patients had morphologic investigation of parathyroid glands by ultrasonography and/or 99m-technetium (^{99m}Tc) sesta-MIBI scintigraphy. It was normal in one patient, whereas the others had a parathyroid adenoma, which was operated successfully in three patients. Surgery showed parathyroid adenoma superimposed on hyperplasia in one case. Nephrocalcinosis was demonstrated by ultrasonography in a hypercalcemic patient.

Renal biopsy

Interstitial fibrosis and tubular atrophy were the most predominant lesions, observed in 24 patients (85%). Moderate arteriosclerosis was present in 24 patients (85%). Fourteen of these had hypertension. Only three patients had severe arteriolosclerosis. The percentage of sclerotic glomeruli ranged from 0% to 90% (median 10%). Only one patient had a lesion of focal segmental glomerulosclerosis (FSGS). Tubular cysts were found in eight patients (28%) and tubular dilatations in 19 patients (66%).

Statistical analysis showed that the degree of interstitial fibrosis did not correlate with the age at renal biopsy (data not shown). On the contrary, the degree of interstitial fibrosis was related to the duration of lithium administration (Table 3) and to the cumulative dose of lithium ($P = 0.045$) (Student t test). Interstitial fibrosis was significantly more severe in patients with the lower creatinine clearance at renal biopsy and at the end of follow-up (Table 3). Tubular dilatations and cysts were more frequent in patients with the longer duration of lithium therapy ($P = 0.027$) whereas these two abnormalities were not predictive of renal function impairment and progression (not shown).

Table 3. Creatinine clearance and lithium therapy duration according to the degree of interstitial fibrosis on renal biopsy

Interstitial fibrosis grading	Creatinine clearance at renal biopsy *mL/min*	Creatinine clearance at last follow-up *mL/min*	Lithium duration at renal biopsy *year*
0 and 1	81.4 ± 23.8	70.9 ± 30.7	6.2 ± 2.9
2 and 3	54.9 ± 23.0	36.7 ± 26.4	10.4 ± 5.7
P value	0.005	0.003	0.02

Mean ± SD; Student t test.

Prospective study

The 14 patients of the Ste. Anne cohort underwent renal biopsy at a mean age of 54.8 years, after a 5 to 8 year lithium administration (cumulative dose 2052.5 g). None had proteinuria. As expected, renal histopathologic changes were mild to moderate. Interstitial fibrosis was graded as two in eight, one in four, and zero in two patients. Mean creatinine clearance was 77.8 mL/min at lithium initiation, 65.2 at renal biopsy, and 40.8 at last follow-up. Mean annual loss of creatinine clearance was −1.93 mL/min. These patients were prospectively followed up during a 18.9-year period. The total mean duration of lithium therapy was 22.8 years, corresponding to a mean total dose of lithium salt of 6905 g. Two patients developed mild hypercalcemia. It is difficult to draw firm conclusions from such a small group of patients. Of interest, however, the final creatinine clearance was 61.3 mL/min in the two patients with grade 0 fibrosis versus 36.0 mL/min in the eight patients with grade 2 fibrosis on renal biopsy, and the only patient who progressed to ESRD had grade 2 interstitial fibrosis on the renal biopsy performed 18 years earlier.

Survey analysis

The questionnaire was answered by 130 dialysis centers. The response rate to the survey was therefore 56%. Among the 10,726 dialysis patients treated in these centers (representing approximately 40% of all dialysis patients in France), 24 had lithium-induced nephropathy (i.e., a prevalence of 0.22% dialysis patients).

At the Necker Hospital between 1989 and 2000, dialysis therapy was initiated in 1391 patients. Two had lithium-induced nephropathy, a percentage of 0.14% among incident dialysis patients.

Figure 3 shows the age distribution of the 24 dialysis patients at the beginning of lithium therapy and at the dialysis initiation, respectively. This figure underlines the

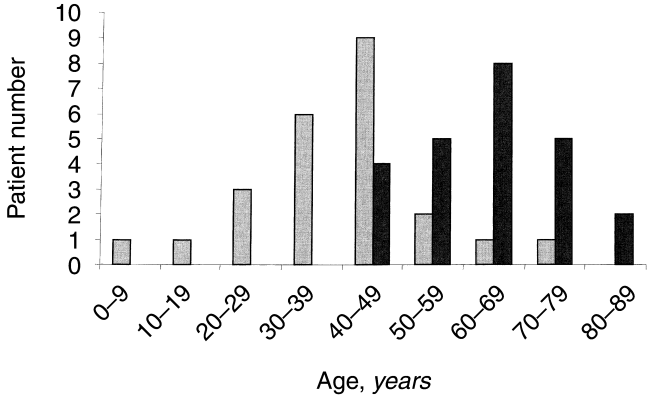

Fig. 3. Survey analysis in 130 French dialysis centers. Age distribution of the patients who progressed to end-stage renal disease (ESRD), at the beginning of lithium therapy (■) and at initiation of dialysis (■).

latency (approximately 20 years) between the onset of the treatment and the need for dialysis therapy.

DISCUSSION

Although the link between lithium and CRF has been disputed in the past [1, 7], it is unequivocally established that long-term lithium administration may induce chronic tubulointerstitial nephropathy leading to renal failure [5, 8]. The present series includes 74 patients treated with lithium for a mean period of about 20 years. Other causes of renal disease were excluded. Creatinine clearance was inversely correlated with the duration of lithium therapy. Similarly, in those patients who underwent renal biopsy, the degree of interstitial fibrosis was related to the duration of lithium administration and with the cumulative dose of lithium salt. Lithium nephrotoxicity may develop chronically in the absence of episodes of lithium intoxication. Less than 50% of the patients had serum lithium concentration above 1 mmol/L at one dosage or more. These results strongly suggest that the duration of lithium therapy and the cumulative dose of lithium are the major determinants of nephrotoxicity.

Lithium-induced nephropathy develops slowly over several decades. This is well demonstrated in the two multicenter studies performed by the same group in Sweden 12 years apart. Only 4% of the patients receiving lithium for a mean duration of 6.5 years had elevated serum creatinine levels, whereas this was found in 12% of the patients after 19 years of administration [12, 13]. In our study, we have been able to estimate the mean annual loss of creatinine clearance in 70 lithium-treated patients, 2.29 mL/min. Unsurprisingly, it is slow as in most chronic renal tubulointerstitial disorders. Of interest, it is close to the decline in GFR recently measured in the African American Study of Kidney Disease and Hypertension, namely 2.07 and 3.22 mL/min per 1.73 m^2 per year in the ramipril and amlodipine groups, respectively [14].

Lithium-induced renal failure may progress to ESRD. A long period of time is needed to reach this stage. This explains why only anecdotal cases were reported in the past [15, 16]. However, in the study by Markowitz et al [8], eight of 24 patients who underwent renal biopsy progressed to ESRD. Of all the patients who underwent renal biopsy in our study, only one reached ESRD. Renal biopsies were performed earlier and the lesions were less severe than in the study by Markowitz et al (e.g., global sclerosis is affecting 20% versus 57.5% of the glomeruli). In our study, regular dialysis became necessary in 12 of 74 patients, at a mean age of 65 years. The estimated cumulative dose of lithium was similar to that of other patients, suggesting that factors other than lithium contributed to progression. These patients had more impaired renal function at entry in the study. Of note, proteinuria was more common in patients who developed ESRD, supporting the suggestion made by Markowitz et al [8] that FSGS is not unusual and contributes to progression in these cases. However FSGS was very rarely found in our patients.

From the survey performed in France, the percentage of lithium-induced ESRD among dialysis patients may be estimated as three per 1000. This value should be considered as a rough and approximate estimation. Indeed, there is no national registry of dialysis patients in France. To our knowledge, lithium-induced nephropathy is identified in only one registry, ANZDATA. In 2000, the incidence rate was 0.7% in Australia (12 cases among 1723 new patients) and 0.2% in New Zealand (1 of 411 new patients), which is slightly higher than in our estimation [17]. In our survey, we have possibly selected centers with well-known patients with lithium-induced nephropathy. Conversely, it is possible that if nephrologists have not paid enough attention to this type of kidney disease, then the reporting could have been underestimated.

It may be expected that interruption of lithium therapy in patients with renal disease has some beneficial effects but also some potential detrimental psychiatric consequences. In patients with established renal disease, it is difficult to demonstrate the beneficial renal effects of interrupting lithium [4]. In 11 patients followed up for more than 1 year before and after interruption, the rate of renal progression was slightly but not significantly less rapid after lithium cessation. In contrast, three patients progressed to ESRD despite interruption. Improvement in GFR has been reported by Aurell and Hestbech [18] after lithium discontinuation in a patient with advanced renal failure but correction of dehydration may have contributed to this improvement. In another study [8], lithium therapy was interrupted in 19 patients with renal disease. Among the nine whose serum creatinine levels were above 220 μmol/L, seven went on to require dial-

ysis, whereas in the 10 others whose serum creatinine levels were below 220 μmol/L, only one progressed to ESRD. Similarly in our study, the probability of renal improvement is higher when estimated creatinine clearance is above 40 mL/min at lithium discontinuation than when it is lower. There is probably a point of no return, where renal fibrosis continues to progress despite suppression of the triggering toxic insult. The psychiatric risk also has to be taken into account despite the availability of other mood stabilizers. Lithium is the first line treatment for the prophylaxis of recurrences in bipolar affective disorder [19]. It is the only compound that has clearly demonstrated antisuicide effects in the maintenance treatment of major affective disorders [20]. Moreover, the risk of early recurrence of bipolar illness appears very high following lithium discontinuation [21]. Besides, some patients, whose illness is well controlled by lithium therapy, refuse to consider interruption and substitution. Therefore, the decision to interrupt lithium and to substitute another drug should involve the patient, the psychiatrist, and the nephrologist. The results obtained in 14 patients who underwent systematic renal biopsy in 1980 and were subsequently followed up are interesting in this regard. The final creatinine clearance is inversely correlated to the severity of renal interstitial fibrosis. Renal biopsy findings might be useful to predict the risk of further progression. Proteinuria is also a marker of poor prognosis. It deserves symptomatic management to retard the progression of FSGS. However, it appears probably late in the course and is not warranted that at this stage, lithium interruption will modify the course of renal disease.

Lithium-associated hypercalcemia, first reported in 1973 [22], has been subsequently ascribed to hyperparathyroidism (HPT) [23]. Up to 25% of lithium-treated patients develop hypercalcemia with increased ionized calcium, independent of plasma volume contraction due to nephrogenic diabetes insipidus [24]. The study by Bendz et al [25] has provided evidence for an increased incidence and prevalence of HPT in patients on very long-term lithium treatment. The incidence of HPT in women of 60 years old or older was approximately three times as high as in women of the general population [26]. As expected, hypercalcemia is aggravated by the development of renal failure, which decreases urinary calcium excretion. In our series, 35% of the patients tested had moderate hypercalcemia due to HPT. One patient with chronic hypercalcemia had nephrocalcinosis, which may have further impaired renal function. No intrarenal calcium deposits, however, were found on renal biopsies. There is a higher proportion (33%) of parathyroid hyperplasia in lithium-treated patients with HPT than in HPT patients of the general population, but parathyroid adenomas still predominate in lithium patients [25–27]. These parathyroid gland lesions explain why lithium withdrawal during an average of 8.5 weeks had no effect on hypercalcemia [25]. The mechanism of lithium-induced HPT remains ill-defined and may involve direct stimulation of PTH production by lithium salts [28], a shift to the right in the set point for PTH secretion [29] and alteration of calcium sensing in parathyroid glands.

Lithium-induced nephrogenic diabetes insipidus has been the subject of many studies. It has been ascribed to inhibition of magnesium-dependent G proteins that activate vasopressin-sensitive adenyl cyclase, resulting in the down-regulation of the vasopressin-regulated water channel aquaporin-2, routed and expressed at the apical plasma membrane of principal cells of the collecting duct [30]. Additional mechanisms have been suggested in lithium-fed rats, increased circulating levels of PTH acting as partial agonist to arginine vasopressin (AVP) and thereby inhibiting its hydro-osmotic action [31], and the down-regulation of urea transporters in the renal inner medulla [32].

In contrast, the mechanism(s) of tubulointerstitial changes is (are) still poorly understood. In lithium-fed animals, tubular lesions, mainly dilatation of tubules, predominate in distal segments and in collecting ducts. Glomerulosclerosis tends to be a late feature [33]. In rats and humans, severe lesions of the mitochondria and endoplasmic reticulum have been documented [6]. In vitro, lithium induces inositol depletion [34, 35] and inhibits cell cycle progression without affecting cell viability, probably via induction of $p21^{Cip}$ [36]. The potential role of these molecular events in lithium nephrotoxicity has to be investigated. Some unknown genetic and/or environmental factors predispose to lithium nephrotoxicity. Indeed, some patients develop very significant renal lesions early in the course of lithium treatment, after 4-year [6], 2-year, and 5-year [8] administration. The proportion of patients who will develop clinically relevant renal toxicity after several decades of lithium therapy, and whether it is restricted to "susceptible" patients, is still unknown. On the other hand, predisposing factors may influence the rate of progression of renal disease and/or renal failure. Epidemiologic studies are required to evaluate long-term renal consequences of lithium therapy. Pathophysiologic studies are also needed to identify these predisposing factors and to understand how they interact with a nephrotoxic substance.

CONCLUSION

Close monitoring of lithium-treated patients is mandatory over the long-term, and close collaboration between psychiatrists and nephrologists should be encouraged on this topic. Monitoring should not only include regular measurements of serum lithium, but also serum creatinine and calcium concentrations. The efficacy of lithium

therapy in the bipolar disorders is so good that some patients are lost to medical follow-up, regular biochemical monitoring is omitted, and renal failure is discovered too late.

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