

# Lithium-induced tardive nephropathy: MRI contribution to the detection of pre-symptomatic renal abnormalities

*Nefropatia tardiva da litio: il contributo della risonanza al rilevamento di anomalie renali presintomatiche*

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## Summary

In patients with insufficient renal function and laboratory evidence of chronic tubulointerstitial nephritis (CTIN) associated to long-term lithium therapy, magnetic resonance imaging (MRI) has been shown to accurately detect the presence of specific renal microcysts, thus allowing confirmation of the clinical diagnosis.

## Objective

We hypothesized that the development of morphological damage evidenced by MRI would precede the impairment of renal functional indices, mainly glomerular filtration rate (GFR).

## Method

To test the hypothesis, we examined 3 consecutive patients treated with lithium for more than a decade and with no signs of renal disease. The patients were specifically selected for showing estimated GFR (eGFR) close to the normal threshold of 60 mL/min/1.73 m<sup>2</sup>.

## Results

Two out of these 3 patients displayed 5-10 renal microcysts measuring from 1 to 2 mm in diameter in each kidney. The patients were a 53 y.o. female and a 48 y.o. male on lithium therapy for 17 and 22 years and with an eGFR of 67 and 63 mL/min/1.73 m<sup>2</sup>, respectively (Table I). Neither patient presented with factors considered to be related to the development of tardive nephropathy, e.g., past episodes of lithium intoxication or elevated serum lithium levels.

## Conclusion

These 2 cases suggest that, in patients on long-term lithium therapy and with eGFR values close to normal limits, MRI may unveil structural renal pathology typical to CTIN in the absence of other signs of disease. Should the findings be substantiated by further observations, MRI may be used to screen for lithium-induced tardive nephropathy in patients at risk (Fig. 1).

## Key words

Long-term lithium therapy • Nephrotoxicity • Renal microcysts • MRI • eGFR

## Riassunto

Nei pazienti con insufficiente funzionalità renale e con prove di laboratorio di nefrite tubulo interstiziale cronica (CTIN) associata a terapia di lunga durata con litio, la RM ha dimostrato di poter individuare con precisione la presenza di specifiche microcisti renali, consentendo così la conferma della diagnosi clinica.

## Obiettivo

Abbiamo ipotizzato che lo sviluppo del danno morfologico evidenziato dalla RM avrebbe preceduto la diminuzione degli indici di funzionalità renale, in particolare la velocità di filtrazione glomerulare (GFR).

## Metodo

Per verificare l'ipotesi, abbiamo esaminato tre pazienti consecutivi trattati con litio per più di un decennio e senza segni di malattia renale. I pazienti sono stati appositamente selezionati per avere una GFR stimata (eGFR) vicino alla soglia normale di 60 ml/min/1,73 m<sup>2</sup>.

## Risultati

Due di questi 3 pazienti hanno presentato in ciascun rene 5-10 microcisti renali della misura 1-2 mm di diametro. I pazienti erano una donna di 53 anni e un maschio di 48 anni, rispettivamente in terapia con litio per 17 e 22 anni e con una eGFR di 67 e 63 ml/min/1,73 m<sup>2</sup> (Tab. I). Nessuno dei pazienti presentava fattori considerati correlati allo sviluppo di nefropatia tardiva, ad esempio, passati episodi di intossicazione al litio, elevati livelli sierici di litio.

## Conclusioni

Questi 2 casi suggeriscono che, in pazienti in terapia di lunga durata con litio e con valori eGFR al limite della norma, ma entro, la RM può svelare una patologia strutturale renale tipica di CTIN in assenza di altri segni di malattia. Qualora questi risultati fossero suffragati da ulteriori osservazioni, la RM potrebbe essere usata per individuare la nefropatia tardiva indotta da litio nei pazienti a rischio (Fig. 1).

## Parole chiave

Terapia di lunga durata con litio • Nefrotossicità • Microcisti renali • MRI • eGFR

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## Introduction

Long-term lithium therapy for bipolar disorder has been mostly associated with two apparently unrelated renal abnormalities: nephrogenic diabetes insipidus (NDI) and chronic tubulo-interstitial nephritis (CTIN)<sup>1-3</sup>. NDI is a common and early side effect that may become chronic, and it is caused by the interference of lithium with the ADH-activated transport of aquaporin-2 to cell membranes in the collecting ducts, therefore decreasing water resorption from the urine<sup>4</sup>. CTIN is a less frequent and late complication that, contrary to NDI which is usually reversible, may be irreversible and further progress to end-stage renal disease (ESRD)<sup>2,5,6</sup>. A recent study suggests that ESRD is an uncommon but not rare consequence of long-term lithium treatment, with a prevalence six times greater than that found in the general population<sup>7</sup>. The average latency between onset of lithium therapy and ESRD, when the latter does occur, is about 20-23 years<sup>6,7</sup>.

Lithium-induced CTIN becomes increasingly common with treatment duration and is revealed clinically by the insidious reduction of glomerular filtration rate (GFR) often in the setting of chronic NDI<sup>2,8,9</sup>. Biopsy findings include areas of tubular atrophy and interstitial fibrosis, both typically in excess to the degree of glomerulosclerosis or vascular disease, with the formation of cortical and medullary tubular cysts, 1-2 mm in diameter, originating from distal and collecting tubules<sup>2,6,10</sup>.

In patients with established nephropathy associated to long-term lithium therapy, magnetic resonance imaging (MRI) has been shown to be an accurate diagnostic tool apt to reveal the presence of characteristic renal microcysts, thus allowing confirmation of the clinical diagnosis of CTIN without the need of renal biopsy<sup>11</sup>. Indeed, MRI is highly capable of defining renal morphological features and has been demonstrated to be superior to US and CT scan for the visualization of small renal cysts<sup>12</sup>.

We reasoned that changes in renal morphology, visible as microcysts at MRI, may precede the impairment of renal physiological indices, and thus wanted to preliminary test this hypothesis by examining patients treated with lithium for more than a decade and with renal laboratory tests within normal limits, i.e. with an eGFR more than 60 mL/min/1.73 m<sup>2</sup> and without any other sign of kidney damage, like persistent microalbuminuria, pro-

teinuria or hematuria (for the current classification of patients with Chronic Kidney Disease based on eGFR, see<sup>13,14</sup>). To improve the odds of positive findings we selected patients with eGFR values between 60 and 70 mL/min/1.73 m<sup>2</sup>. A preventive approval of the Institutional Review Board was not required for this case study. Nevertheless, patients signed an informed consent in relation to the MRI procedure and to authorize the publication of data under anonymity.

Here we report on 2 patients, out of the first 3 consecutively examined at the time of this writing, in whom renal microcysts measuring from 1 to 2 mm in diameter were detected.

## Case reports

Main clinical features of the 2 patients are summarized in Table I. Demographic and clinical information was obtained by retrospect review of each patient's medical charts and registration of serum lithium values from the onset of treatment up to the evaluation time. Maximal serum lithium was listed; both average serum lithium level and average lithium dose over the entire treatment were calculated.

Neither patient had past episodes of lithium intoxication, cardiovascular disease, somatic illness of import, or a family history of cystic kidney disease. Both patients were receiving thyroid supplementation and concomitant psychotropic medications (valproic acid and quetiapine, respectively).

GFR mL/min/1.73 m<sup>2</sup> was estimated from the four-variable Modification of Diet in Renal Disease study equation with the use of calibrated serum creatinine levels<sup>15</sup>. In order to increase the reliability of measurement<sup>13</sup>, serum creatinine was appraised twice according to routine laboratory methods, the two blood samples consecutively assessed within a week, and the values reported are the mean of two assessments. Urine volume (mL/24 h) was based on a single assessment. Routine laboratory methods ruled out microalbuminuria, proteinuria or hematuria.

MRI was performed with a 1.5-T MRI unit with gadolinium-enhanced sequences.

Both patients had normal-sized kidneys with 5 to 10 homogeneously distributed parenchymal microcysts in each kidney. On T2-weighted images, the microcysts typically appeared as hyperintense little areas; on T1-weighted images, after enhancement of the renal parenchyma with contrast ma-

**TABLE I.**

Demographic and clinical features of patients and renal findings. *Caratteristiche cliniche e demografiche dei pazienti e reperti renali.*

	Patient # 1	Patient # 2
Sex	Female	Male
Age (years)	53	48
Education (years)	19	18
Diagnosis	BPI	BPI
Age of onset of illness (years)	25	21
Number of episodes	7	16
eGFR (mL/min/1.73 m <sup>2</sup> )	67	63
Serum creatinine (mg/dL)	.93	1.29
RENAL MRI FINDINGS		
Number of microcysts (R/L kidney)	R6/L10	R5/L5
URINE ANALYSIS		
Volume (mL/24 h)	2,750	1,500
Microalbuminuria (24 h)	< 8 mg	< 8 mg
Hematuria	absent	absent
Protenuria	absent	absent
LITHIUM THERAPY		
Length of therapy (years)	17	22
Average serum level (meq/L)	.71	.68
Maximal serum level (meq/L)	1.02	1.18
Average Li <sub>2</sub> CO <sub>3</sub> dose (range) (mg/die)	845 (600-900)	1,017 (900-1,450)

terial, the renal microcysts appeared as nonenhanced hypointense (dark) round areas, measuring 1 to 2 mm in diameter (Fig. 1).

## Discussion

These 2 cases suggest that very long-term lithium therapy may be associated with structural renal pathology typical to CTIN, i.e. microcysts, even if GFR estimates are greater than 60 mL/min/1.73 m<sup>2</sup> and there is no other sign of kidney damage. The fact that these 2 cases belong to a sample of 3 does not mean that 2/3 of patients on long-term lithium therapy have similar findings. Certainly, 2/3 of patients on long-term lithium therapy do not develop CTIN. The sample studied is highly biased in that it was intentionally selected on the basis of an eGFR only slightly higher than 60 mL/min/1.73 m<sup>2</sup> threshold value. Thus, the findings of the study

may apply only to patients on long-term lithium therapy whose eGFR is at the edge of normality.

The MRI pattern displayed by our patients is characteristic of lithium-induced nephropathy<sup>11</sup>. In the study by Farres et al.<sup>11</sup>, patients had normal-sized kidneys with uniformly and symmetrically distributed renal microcysts, from abundant, as in most cases, to sparse (< 10), as in a minority of cases. In concordance to this report, our patients had normal-sized kidneys, and displayed "sparse" microcysts, 1-2 mm in diameter, uniformly located within the parenchyma. These features, within the clinical context of long-term lithium therapy, are typical of lithium-induced tardive nephropathy, and allow a differential diagnosis from health and other cystic diseases. In the healthy population aged 45-59 years, the average number of simple cysts detected by MRI is less than 2<sup>16</sup>. In Autosomal Dominant Polycystic Kidney Disease



**FIGURE 1.**

T1-weighted image of left kidney in a 53 y.o. female. After enhancement of the renal parenchyma with contrast material, renal microcysts (1-2 mm) appear as nonenhanced hypointense (dark) round structures in the lateral middle-upper pole and in the medial lower pole. *Immagine della risonanza del rene sinistro pesata in T1 in una donna di 53 anni. Dopo accentuazione della trama parenchimale renale con mezzo di contrasto, le microcisti renali di 1-2 mm appaiono come strutture rotondegianti non accentuate, ipointense (scure) nel polo laterale medio superiore e in quello medio inferiore.*

the kidneys are usually enlarged and the renal cysts are variable in size and signal intensity<sup>17</sup>. In Glomerulocystic Kidney Disease cysts are exclusively located in the renal cortex and patients are usually children<sup>18</sup>. Medullary Cystic Kidney Disease develops with chronic renal failure, the cortex is thin and the cysts are in the medulla and corticomedullary junction<sup>19</sup>. Acquired cystic kidney disease results from the development of renal cysts in patients who have advanced chronic renal failure or who are undergoing dialysis<sup>20</sup>.

It is worthy of notice that the patients were not particularly old, nor did they have episodes of lithium intoxication, somatic illness, or particularly elevated maintenance serum lithium levels, factors all considered to be related to the development of tardive nephropathy<sup>21,22</sup>. Time on lithium was the only identified risk factor in our patients.

As lithium is generally considered to be the gold standard for maintenance therapy in bipolar disorder<sup>23</sup> and is widely used in this population for long time, if not lifetime, our finding may have clinical relevance, provided that further studies were to

confirm the presence of renal disease in lithium-treated patients that would be considered healthy otherwise. MRI may then be used for an early diagnosis of lithium-induced tardive nephropathy thus increasing the odds of renal improvement upon lithium discontinuation or lowering.

In patients with established renal disease, it may be difficult to demonstrate the beneficial renal effects of discontinuing lithium<sup>23</sup>. There is probably a point of no return, where interstitial fibrosis continues to progress despite discontinuation of treatment. In one study<sup>2</sup>, despite discontinuation of lithium, only 3 patients out of 15, all with initial serum creatinine < 2.1 mg/dL, had subsequent improvement in renal function, while 7 of 9 patients with initial serum creatinine values > 2.5 mg/dL progressed to ESRD. Similarly in another study, the probability of renal improvement at lithium discontinuation was higher when estimated creatinine clearance was above 40 mL/min than when it was lower<sup>6</sup>.

The clinical implications of demonstrating the presence of renal structural lesions in patients on long term lithium therapy are not straightforward, even though lowering or discontinuing lithium with further monitoring of renal function would seem a sound choice. However, lithium discontinuation, and probably any abrupt fall in serum lithium levels, may trigger a recrudescence of psychiatric illness<sup>25,26</sup> and increase overall morbidity and suicidal behavior in particular<sup>27</sup>. Thus, any major modification of lithium therapy should be carried out very carefully and only under the supervision of clinicians experienced in managing bipolar disorders.

In conclusion, our cases suggest that, in patients on long term lithium therapy with no signs of renal disease but with eGFR values slightly over 60 mL/min/1.73 m<sup>2</sup>, MRI may detect structural renal pathology typical to CTIN, i.e., microcysts, 1-2 mm in diameter. Where the findings substantiated by further observations, MRI may be used to screen for lithium-induced tardive nephropathy in patients at risk.

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