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Case Report

Nephrotic syndrome during lithium therapy

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Introduction

Lithium salts are a commonly used and quite effective therapy for unipolar and bipolar affective disorders. The more commonly reported renal side-effects during long term lithium therapy are nephrogenic diabetes insipidus, chronic interstitial nephropathy, and renal tubular acidosis [1].

The nephrotic syndrome is a rare but recognized complication of lithium therapy which was described the first time in 1973 by Duflot *et al.* [2]. A comprehensive search of the world literature shows that 19 cases have been reported to date [2–16]. These cases have been associated with different glomerular lesions such as minimal-change disease, membranous nephropathy, or focal glomerulosclerosis. In general this complication is observed during the first year of lithium therapy but we report the case of a woman who developed a nephrotic syndrome after 20 years of lithium therapy and in which the nephrotic syndrome rapidly and completely disappeared after withdrawal of lithium without need of steroid therapy.

Case report

A 40-year-old white Caucasian female was referred to our hospital because of a nephrotic syndrome. She had been on lithium therapy for 20 years because of an affective disorder. Her lithium levels had always been within the therapeutic range, with normal creatinine levels and without proteinuria. A few days before admission, she consulted her practitioner because of generalized oedema. A nephrotic syndrome was diagnosed and the patient was referred to our hospital for further investigations. On admission, her medication consisted of imipramine (Tofranil®) 25 mg t.i.d., temazepam (Normison®) 2.5 mg t.i.d., lithium carbonate (Lithiofor®) 600 mg b.i.d. and frusemide (Lasix®) 40 mg/day.

The patient was in good general condition. Her temperature was 37.5°C, blood pressure 110/70 mmHg, and the heart rate was 90 beats per min. Pitting oedema of the face and legs (2+) was present. The physical examination was otherwise unremarkable. Laboratory results included sedimentation rate 118 mm/h, haemoglobin 153 g/l, haematocrit 0.45, leukocytes 8.9 g/l, thrombocytes 285 g/l, total protein 51 g/l, serum albumin 22 g/l, blood urea 4.7 mmol/l, serum creatinine 75 μmol/l, sodium 141 mmol/l, serum potassium 4.7 mmol/l, total cholesterol 11.4 mmol/l, serum lithium 0.43 mmol/l (normal range 0.3–1 mmol/l). The 24-h urine collection contained 16 g of proteins (82% albumin) without Bence Jones proteins. Creatinine clearance was 65 ml/min. Urinalysis showed 3–5 erythrocytes and 3–5 leukocytes. Urinary concentration of sodium was 5 mmol/l and of potassium 28 mmol/l. Serology for HBV, HCV, and HIV was negative. Rheumatoid factor, ASLO, antinuclear and anti-DNA antibodies were also negative. Ultrasonogaphic examination showed moderately enlarged kidneys and a percutaneous renal biopsy was performed.

Light-microscopy examination of the biopsy revealed glomeruli without any significant morphological abnormality. There were two small foci of tubular atrophy and interstitial inflammation. Electron-microscopy showed diffuse epithelial cell foot process fusion without any electron-dense deposit. The histological findings fulfilled the diagnosis of minimal-change disease. Direct immunofluorescence showed slight finely granular deposits of IgG and IgM in the glomeruli, with predominant mesangial localization. There were no deposits of IgA, C3c and fibrin/fibrinogen.

The diagnosis of minimal-change disease secondary to lithium carbonate therapy was considered and the drug was discontinued. Within 6 weeks after cessation of the drug we observed a complete remission of the nephrotic syndrome (proteinuria < 100 mg/day).

Discussion

Mild proteinuria is commonly seen after 2 years of lithium carbonate therapy [1] but the nephrotic

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syndrome is very rare. We carried out a comprehensive search of the world literature with MEDLINE on the last 25 years with an analysis of cross-references. We found nineteen reported cases [2–16]. Strictly speaking the demonstration of a relationship between a drug and a clinical adverse event include (1) the appearance of the side-effect during the therapy, (2) its regression after drug discontinuation, and (3) the reappearance of the same adverse event after a new challenge. It should be noted that these strict diagnostic criteria (including a new challenge with the drug followed by recurrence of the nephrotic syndrome) were fulfilled in only four of the cases reported in the literature. Noteworthy in all these four cases the reintroduction of lithium therapy was indicated for therapeutic reasons (i.e. psychiatric symptoms) and not for diagnostic purposes [5–7,13]. In most cases the rapid remission of the nephrotic syndrome after lithium discontinuation was considered to be sufficient to support the link between lithium therapy and nephrotic syndrome—as we did in our case.

We summarized some clinical and biological data concerning the reported cases in Table 1. This table shows that both genders were equally represented and that the age of the reported cases varied from 14 to 78 years. At the time of diagnosis the 24-h proteinuria varied from 3 to 69 g/day and in all but five cases the lithium levels were within the therapeutic range. In the majority of these cases (12/19, 63%) the nephrotic syndrome became apparent during the first year after the introduction of lithium therapy, but in a few it developed after more than 10 years of treatment. Our patient was managed with lithium for 20 years before the nephrotic syndrome developed and this is the longest period reported to date.

Table 1 shows that among the 20 cases reported, 17 (nos 1–17) had a similar and quite typical clinical course with the onset of a nephrotic syndrome while under lithium therapy and a rapid remission of the nephrotic syndrome after discontinuation of the drug—generally within 2–6 weeks. Four of these patients were treated with steroids to hasten the recovery, but for the majority steroids were not necessary to achieve complete remission. The case reported by Singer *et al.* (no. 17) is particularly interesting. In this patient the lithium therapy could not be discontinued because of severe psychiatric symptoms but a complete remission was achieved with a course of 4 months of low-dose azathioprine (0.6 mg/kg/day) without any recurrence of nephrotic syndrome during a 12-year follow-up [14,17]. A renal biopsy was performed in 15 of these 17 cases. In 13 cases the pathological diagnosis was minimal-change disease, while the two others had membranous nephropathy [13,14]. Eight of these 17 cases also had acute renal failure (ARF) along with the nephrotic syndrome. In two of them the ARF was related to acute tubular necrosis, in five the ARF was prerenal, and in the last case the ARF was probably related to concomitant acute lithium intoxication [2]. In all these patients the renal function recovered and none of them developed chronic renal failure (follow-up of 1 to 144 months). As indicated above, in four patients lithium had to be reintroduced due to worsening of psychiatric symptoms [5–7,13]. The nephrotic syndrome recurred in all patients within a few weeks following the reintroduction. In two of them an alternative psychiatric treatment could be given—with a new remission of the nephrotic syndrome [6,13]. In the two remaining patients this was not possible and long-term steroid therapy was given—with clinical improvement but persistence of a significant proteinuria [5,7]. These observations emphasize the high risk of recurrence in patients having already developed a nephrotic syndrome under lithium therapy.

The three last cases reported in Table 1 (cases no 18–20) had a quite different clinical course [15,16]. All developed chronic renal failure. These cases were remarkable for a quite different clinical presentation as well as for the glomerular lesions—with diffuse or focal glomerulosclerosis which were accompanied in two cases by severe interstitial fibrosis. These three cases were also particular by the fact that lithium therapy was pursued for a long period despite signs of renal involvement well before the development of the nephrotic syndrome. Case 18 already had a marked chronic renal insufficiency (creatinine 370 μmol/l) 3 years before the development of the nephrotic syndrome but lithium therapy had nevertheless been continued. Case 19 already had a chronic renal insufficiency when the nephrotic syndrome developed. In these two cases the renal insufficiency was probably related to the presence of severe interstitial lesions. The nephrotic syndrome partially regressed after discontinuation of lithium, while the renal function only slightly improved. Case 20 had a significant proteinuria (dipstick 3+) 3 years before the nephrotic syndrome developed and the renal biopsy was performed. After the biopsy the lithium therapy was not discontinued (a converting enzyme inhibitor was prescribed) and over the following 10 months the patient developed progressive renal failure, worsening nephrotic syndrome, and inferior vena cava occlusion, and died of pulmonary embolus [16]. In these three cases the relationship between lithium therapy and the glomerular lesions is less evident. The glomerulosclerosis may also have been secondary to the interstitial damage, possibly associated to long-standing treatment with lithium. Therefore whether glomerulosclerosis reflects a longer duration of the disease, a distinct primary lesion or a secondary lesion remains unclear for these cases.

Little is known about the mechanism by which lithium can cause the nephrotic syndrome and minimal-change disease. Some authors theorized that lithium could interact with anionic sites of the glomerular capillaries known to limit the passage of macromolecules and thus cause proteinuria [3,6]. This would not explain why other cations similar to lithium do not cause similar problems. There is evidence that minimal-change disease is associated with abnormal lymphocyte function. Since lithium has been demonstrated to modulate lymphokines production by T-cells,

Table 1. Summary data concerning the 20 cases° of nephrotic syndrome (NS) during lithium therapy that have been reported in the literature

Patient no.	Reference	Sex	Age (years)	Duration of lithium therapy (months)	Proteinuria (g/day)	Creatinine (μmol/l)	Renal biopsy	Remission of NS after lithium withdrawal	Use of steroids	Follow-up (months)	Chronic renal failure
1	2	F	62	7	10	'ARF'	MCD	Complete	No	1	No
2	3	F	14	3	3	71	MCD	Complete	No	2	No
3	4	F	78	96	69	256	MCD + ATN	Complete	Yes	24	No
4	4	F	38	48	7	204	MCD + ATN	Complete	Yes	4	No
5	5	M	56	8	32	735	MCD	Complete*	No**	9	No
6	5	F	28	3	15	<125	MCD	Complete	No	18	No
7	6	F	23	6	7	200	MCD	Complete*	No	108	No
8	7	M	49	10	21	<125	MCD	Complete*	No**	24	No
9	8	M	63	3	12	364	MCD	Complete	No	12	No
10	9	F	60	1	9	<125	MCD	Complete	No	1	No
11	10	M	41	6	11	95	MCD	Complete	Yes	2	No
12	PS	F	40	240	16	75	MCD	Complete	No	2	No
13	11	M	35	12	12	170	MCD	Complete	Yes	1	No
14	11	F	55	8	>3	160	Not done	Complete	No	2	No
15	12	F	19	2	23	80	Not done	Complete	No	1	No
16	13	M	47	47	9	120	MN	Complete*	No	36	No
17	14	M	58	144	4	?	MN	Not stopped	AZA	144	No
18	15	F	36	156	4	671	IF + DGS	Partial	No	1	Yes
19	16	F	38	168	10	248	FSG + IF	Partial	No	12	Yes
20	16	M	41	?	8	80	FSG	Not stopped	No	10	Yes

°Note: one of the three cases reported by Santella *et al.* [16] is not included as the patient had stopped taking lithium 5 years before the NS developed.
MCD, minimal-change disease; MN, membranous nephropathy; IF, interstitial fibrosis; DGS, diffuse glomerulosclerosis; FSG, focal segmental glomerulosclerosis; ATN, acute tubular necrosis; ARF, acute renal failure; PS, present study.
*Cases in which the lithium therapy had to be reintroduced and in which the nephrotic syndrome recurred. **Recurrence treated with steroids.
AZA, remission after 4 months of low-dose azathioprine (0.6 mg/kg/day) while lithium continued; no recurrence after 12 years [17].

Tam *et al*. [4] suggested that lithium could enhance permeability factor release by T cells by interacting with intracellular second messenger pathways and thus promote proteinuria.

Given the potentially harmful consequences of lithium therapy, screening for renal damage seems appropriate. Wallin *et al*. [18] showed a link between loss of kidney concentrating capacity and the development of renal damage. They proposed urinary concentration test as the most suitable test for detection of kidney lesions and reduced glomerular filtration rate in long-term lithium treatment. Proteinuria was not considered in that study. Urinary dipstick for the detection of proteinuria is convenient, cheap, and sensitive but gives no information on renal function. Accordingly, both renal function tests and/or urinary concentration tests and dipstick should be performed regularly for early detection of kidney damage. The extent to which long-standing mild proteinuria can be tolerated under lithium therapy is, however, not known.

In summary lithium-induced nephrotic syndrome is very rare. In a majority of cases it develops in patients having therapeutic blood levels of lithium during the first year of therapy, but may appear after up to 20 years of lithium treatment. In most cases it is due to minimal-change disease, and the patient generally recovers rapidly after discontinuation of lithium, without the need of steroids. There is, however, a high risk of relapse if lithium therapy is resumed. Accordingly we consider that the use of steroids should be reserved for the (rare) patient with persistent nephrotic syndrome despite the discontinuation of lithium or for those in which lithium cannot be stopped because of the psychiatric symptoms. Alternatively a short course of low-dose azathioprine may be quite effective and should be considered [14,17]. Careful screening of the urinary status and renal function before and during lithium therapy is highly recommended. A mild proteinuria may probably not be an indication to stop the drug, but for a closer monitoring of the urinary status and renal function.

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