

LITHIUM AND KIDNEY¹
(A study of renal biopsy in Lithium patients)

A. VENKOBA RAO²,
A. SUGUMAR³,
N. HARIHARASUBRAMANIAN⁴,
A. V. SHANTI⁵,
K. RAMACHANDRAN⁶ AND
C. L. ASHOK KUMAR⁷.

SUMMARY

A study of renal biopsy in 13 lithium treated patients is reported. The light microscopic changes were non-specific and comprised glomerular hypercellularity; cloudy swelling of the tubular epithelium and interstitial fibrosis. Correlation between structural changes and functional alterations could not be established. The duration of therapy did not have any bearing on the intensity of the structural changes. No case of renal failure occurred in well controlled series as ours.

The widespread use of Lithium in affective disorders especially in their prophylaxis has necessitated a careful assessment of renal structure and function in view of its reported nephrotoxic properties. Of late this has become an area of intense interest.

Animal Studies :

A few reports of renal damage due to lithium toxicity in experimental animals are available. Epithelial degeneration and dilatation of the distal part of the nephrons have been induced in dogs by Radomski *et al.* (1950). Degenerative changes in the proximal convoluted tubules in rats have been demonstrated by Schou (1958). Evan and Ollerich (1972) have shown ultrastructural lesions in lithium treated rats with blood levels corresponding to the therapeutic range in the humans. They are characterised by an initial mitochondrial change with bulging of cytoplasm of the tubular cells followed by liquefaction,

Karyolysis and karyorhexis of the distal convoluted tubules and the collecting ducts.

Human Studies :

The published reports on renal studies have revealed glomerular as well as tubular dysfunction. Serum creatinine, creatinine clearance, Cr EDTA clearance, B₂ microglobulin excretion have been employed to test the integrity of the glomerular function while 24-hour urinary volume, ability for acidification, urine AVP assay, osmolarity and tubular proteinuria are applied for testing tubular functions (Hallgren *et al.*, 1979; Hullin *et al.*, 1979; Venkoba Rao, *et al.*, 1979).

The structural changes in the kidneys of patients on lithium have now been described and these are classifiable as (i) specific lesions due to lithium and (ii) Non-specific lesions. These latter though, occurring in lithium treated patients are noticeable also under other situations.

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²Institute of Psychiatry,

³Department of Physiology,

⁴Department of Pathology,

⁵Department of Urology,

Madurai Medical College and Govt. Rajaji Hospital, Madurai-625 020.

Specific Renal Lesions :

The essential pathology is tubular in distribution and is restricted to the distal convoluted tubules and collecting ducts. The ultrastructural changes comprise apparent swelling of the cytoplasm and mitochondria with the other intracellular organelles at the periphery of the cells. No cell necrosis is seen. These changes occur within a few days of the starting of lithium and are pharmacological rather than toxic in nature. They are reversible and are not seen following the cessation of therapy for a year. (The lithium ion is known to interfere with the action of Adenyl cyclase in the formation of cyclic AMP). The location of the lesions is where the vasopressin receptors are thought to be and this lesion presumably is the basis for the "Arginine vasopressin resistant diabetes insipidus syndrome." This so-called "unique" lithium lesion has been reported from Australia by Burrows *et al.* (1978), appropriately so when Cade, an Australian gave us earlier lithium for use in MDPs.

Non-specific renal lesions :

Hestbach *et al.* (1977) described first what they believed to be the irreversible morphological lesion due to lithium and suspected them to be progressive. However, Davies and Kincaid-Smith (1979) have found that the changes occur not only in patients receiving lithium but also in those about to receive it. These non-specific changes consist of (i) glomerular sclerosis, (ii) tubular atrophy, (iii) interstitial fibrosis and (iv) cast formation.

PRESENT STUDY

The Lithium clinic has been functioning in the Institute of Psychiatry, Govt. Rajaji Hospital and Madurai Medical College, Madurai, for several years now and presently there are 105 patients on its rolls (M=79 ; F=26). The age structure varied from 10 to over 70 years. The duration of

treatment extended from a minimum of one year to over five years. The dose of lithium ranged from 750 mg. to 1500 mg. a day. The serum lithium levels were between 0.6 to 1.0 mEq./Lit. Earlier a report on renal functioning in lithium treated patients from the clinic has been published (Venkoba Rao *et al.*, 1979).

AIMS

The aims of the study were—

- (i) to analyse the structural pathology of the kidneys of the patients receiving lithium ; and
- (ii) to correlate these with renal functional abnormalities and the duration of treatment with lithium.

MATERIAL AND METHOD

Thirteen amongst the 105 lithium patients attending the Lithium clinic, Institute of Psychiatry were chosen for renal puncture biopsy. They gave their willing consent for the procedure, which was carried out by one of us (CLA). The criterion for selection for biopsy was administration of lithium for more than a year; the duration of treatment in these cases varied from 1.25—5 years. Eleven fell under this category. In the other two, lithium was withheld by us for a period of 7 and 8 months after a continuous administration for 2 and 2.5 years respectively. A preliminary plain picture of abdomen to visualise the life of the kidneys was taken in all the patients. They all went through the battery of renal function tests which have already been reported and mentioned earlier (Venkoba Rao *et al.*, 1979). The biopsy tissue was examined under light microscopy with suitable stains. Excepting for post biopsy hematuria lasting for 24-48 hours in a few cases no other complications were observed in our series.

OBSERVATIONS

The histopathological changes observed

were as follows :

- (i) Glomerular hypercellularity (N=4) (Fig. 1).
- (ii) Cloudy swelling of the tubules (N=2) (Fig. 2).
- (iii) Interstitial fibrosis (N=3) (Fig. 3)
- (iv) No changes were seen (N=4).
(Normal renal appearances).

Of the two patients who were off lithium, one showed glomerular hypercellularity and another, normal appearance. The three other patients who showed normal renal appearances were on lithium for 1.25—5 years. The other pathological changes were all evident in patients who were continuing lithium.

The intensity of the microscopic changes does not seem to be proportionate to the duration of lithium administration. This is brought out in Table 1.

TABLE-1

Pathological Changes	No. of cases	Duration of lithium therapy
1. Glomerular hypercellularity.	4*	3.5—5 years
2. Cloudy swelling of tubules.	2	2.5—3.5 "
3. Interstitial fibrosis	3	2.5—3.5 a,,
4. No change	4*	1.25—5 "

*One was "off" lithium.

An analysis was made of the correlation between renal function test findings in these cases and histopathological changes. The analysis failed to reveal any sort of correlation. For example : Mrs. A who had low hydrogen ion excretion which is a tubular function was free from tubular pathology but showed glomerular hypercellularity and interstitial fibrosis. Mrs. M who had polyuria which again is a tubular function had only glomerular hypercellularity.

DISCUSSION

That renal changes set in both structurally and functionally in lithium consumers has been established. However, the percentage of patients developing this untoward effect is no higher than 12-15% and no lower than 6-8% (Rafaelsen, 1980). Though renal damage resulting in death from renal failure has been known to occur during lithium intoxication (Chapman & Lewis, 1972) no mortality among lithium receivers under controlled conditions has so far been reported (Hallgren *et al.*, 1979 ; Vestergaard *et al.*, 1979). In our earlier report (Venkoba Rao *et al.*, 1979) glomerular function was found to be normal while tubular concentrating and acidifying ability were decreased. These changes were not severe enough to warrant discontinuation of treatment. Our study confirmed polyuria and polydipsic action of lithium. Glen and his colleagues (1979) showed that there was no increase in mortality in a series of 810 patients exposed to lithium over a period of ten years compared to expectation. Lithium is definitely contraindicated in patients who have a poor renal function and in those with a history of nephritic problems (Lancet, 1979a). A complete initial assessment of renal function in prelithium stage and its periodic repetition is mandatory. It has been hypothesized that a 24-hour urine volume around 4000 cc., 24-hour creatinine clearance below 1.0 ml/sec (60 ml/min) and serum creatinine level of over 1.5 mg. per 100 ml. are indications for discontinuance of lithium. A 24-hour thirst test is also recommended after consultation with nephrologist (Rafaelsen, 1980).

But what about the changes in the renal architecture under lithium ? Are they due to lithium ? It was thought to be so when Hestbach and her co-workers (1977) reported chronic renal lesions in 13 patients treated with lithium for 1.5 to 14 years. In 8 of them the lithium intoxication was

acute and other 5 had severe polyuria. However, subsequent work by Kincaid-Smith *et al.* (1979) demonstrated that such changes were non-specific in nature and occurred in prelithium patients and also in patients receiving other neuroleptics. Hence, the evidence seems to be that lithium could be exonerated to some extent. The pathological lesions observed in our thirteen cases fall under the non-specific types.

Certain theories have been advanced to explain the renal lesions that tend to allay the apprehension over lithium nephrotoxicity. It is held that kidneys share the cardio-vascular changes that the MDPs are liable to and it is known now that the mortality amongst the MDPs is high from cardiovascular diseases (Glen *et al.*, 1979). Nevertheless the renal lesions do not appear to be arteriosclerotic in nature. It has also been suggested that the renal lesions may be due to a hypersensitivity response in patients with MDP and lithium, as any other drug may have just precipitated them. Hypothyroid state has also been invoked to explain the abnormal renal function, since such associational changes have been observed by Katz *et al.* (1975) and Salomon *et al.* (1967). However, Hallgren *et al.* (1979) have disproved this. In our series, there was one patient with hypothyroidism who showed normal renal appearance. Finally electrolyte abnormalities have been described in a group of affectively ill patients and these may stem from renal pathology itself, not related to lithium exhibition (Coppen, 1970). Hence, the prevalent view appears to be that much more researching is needed before the renal dysfunction and pathology could be attributed to lithium *per se*.

In this context, the report of Hullin and others (1979) merit mention. A comparative study between lithium treated and control patients (on psychotropic other than lithium) failed to reveal any significant renal impairment in lithium group. Our observations that there is no correla-

tion between the renal function and structural changes find support in the report of Burrows *et al.* (1978) who showed a normal serum creatinine and a normal urine in spite of impressive morphological change in their material. Vastergaard *et al.* (1979) suggest that lithium induced kidney changes may be made less frequent if the patients are maintained on doses lower than the currently accepted levels as therapeutic but they caution this may jeopardise the expected prophylactic benefit. To suggest renal biopsy either before, during or after lithium therapy is a tall order since it is neither feasible nor practical and falls under an invasive investigation. We know that the prophylactic effect becomes operative after administration of lithium for 12-18 months. It is also important in this connection to note that the so-called therapeutic window, i.e., the gap between the therapeutic and toxic dose is narrow for lithium. Under such circumstances, a careful selection of cases, thorough urological assessment and periodic repetition of tests become absolutely necessary. Appropriate measures to avoid lithium intoxication during infections, fluid loss and dehydration are to be instituted. There is no alternative to this until a clear cut picture emerges exonerating lithium in the genesis of renal damage. An attitude of "cautious optimism" as advised by Lancet (1979b) is called for at present. Under well organised and controlled conditions, lithium continues to be safe, a consensus arrived at the meeting of the Biological Psychiatry Section of W.P.A. on "Lithium treatment and Kidney damage" held at Copenhagen, October, 1979.

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