Permanent Neurological Sequelae Despite Haemodialysis for Lithium Intoxication

B. VON HARTITZSCH, N. A. HOENICH, R. J. LEIGH, R. WILKINSON, T. H. FROST, A. WEDDEL, G. A. POSEN

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Summary

Three patients with lithium toxicity are reported, two of whom were exposed to toxic lithium levels for a prolonged period: both survived with permanent damage to basal ganglia and cerebellar connexions despite effective lowering of lithium levels by haemodialysis. Data obtained during dialysis treatment show prolonged haemodialysis to be the treatment of choice. If facilities for haemodialysis are not available or the patient presents with toxic lithium levels and minimal symptoms peritoneal dialysis will effectively lower serum lithium levels, but more slowly than haemodialysis.

Introduction

The increasing use of lithium in the treatment of manic depressive (Wharton and Fieve, 1966; Baastrup and Schou, 1967; Coppen *et al.*, 1971) and recurrent depressive (Zall *et al.*, 1968; Fieve *et al.*, 1968; Baastrup *et al.*, 1970) disorders will increase the chances of lithium intoxication. There is little latitude between effective therapeutic levels of less than 1·5 mEq/l. (Zall *et al.*, 1968) and toxic levels of 1·6 mEq/l. or greater (Schou *et al.*, 1968; Zall *et al.*, 1968) in the early stages of treatment, but thereafter therapeutic effects can be maintained with lower levels of 0·3-0·8 mEq./l. (Zall *et al.*, 1968). Many of the treated patients are in an older age group in which an increased incidence of renal impairment (McCance, 1962) as well as decreased handling of lithium by the kidney (Schou and Baastrup, 1967) could be important contributory factors to lithium intoxication. The features of lithium intoxication have been well documented by Schou *et al.* (1968) and, in general, patients have either died or recovered completely with no lasting neurological sequelae (Schou *et al.*, 1968).

We describe two cases of lithium intoxication treated by haemodialysis and one treated by peritoneal dialysis. The two treated by haemodialysis presented for dialysis treatment after explosure to toxic lithium levels of several days, and as a result survive with permanent and disabling neurological sequelae. Data obtained during these treatments compounded with data from a previously described case (Amdisen and Skoldborg, 1969) enable us to make recommendations on timing and duration of dialysis therapy.

Case 1

A 50-year-old woman was started on lithium carbonate 800 mg daily in addition to small doses of chlorpromazine 100-200 mg daily. Two days later, seven days before admission, lithium carbonate was increased to 1,600 mg daily (400 mg four times a day), the next day to 2,400 mg, and thereafter it was reduced to 1,600 mg daily. Three days before admission to hospital she was drowsy, nauseated, and vomiting but the medications were continued and the next day she was lethargic, ataxic, and had difficulty in walking. Two days later, on the day of admission, she could not sit unaided, she became unresponsive, and had three grand mal seizures. She was stuporous, responding to painful stimuli only by opening her eyes, and showed generalized hyper-reflexia and bilateral extensor plantar responses. Her hydration was good and blood pressure was 100/70 mm Hg. The serum lithium level was 5 mEq/l.

Peritoneal dialysis was started and during five cycles the serum lithium fell to 2·5 mEq/l. but her condition deteriorated. Haemodialysis on an Ultraflo 100 coil via Seldinger catheters began seven and a half hours after the start of the peritoneal dialysis. She had four hours of haemodialysis during which she experienced hypotension unresponsive to intravenous fluids, deepening coma, and shallow inadequate respirations for which she required artificial ventilation. The post-dialysis lithium was 1·5 mEq/l. Her urine output was low and the serum urea and creatinine rose to 60 mg/100 ml and 4 mg/100 ml respectively but thereafter improved. She experienced frequent episodes of generalized seizures which persisted through to the eighth day, in spite of further four- to six-hour haemodialyses on the 3rd, 4th, and 6th hospital days which effectively lowered her serum lithium level to less than 0·2 mEq/l. The cerebrospinal fluid was under normal pressure, free of cells, and cerebrospinal fluid protein and sugar levels were normal. Spontaneous respirations started on the eighth day.

Her state of consciousness improved over the next few days when she developed a flapping tremor of her left hand, constant fluttering of her eyelids, pursing of her lips, and frequent involuntary movements of extrapyramidal type involving both right and left arms. She also had bilateral nystagmus and features suggesting some cerebellar ataxia involving the right side. Despite some initial improvement she was ataxic with frequent choreoathetoid movements one year later.

Case 2

A 53-year-old woman was started on lithium carbonate 1,600 mg daily, and four weeks later she began to vomit, developed slurred speech, and became mildly ataxic. Her serum lithium level was 2·3 mEq/l., and further lithium was withheld. She deteriorated, became disorientated, unable to feed or walk because of the ataxia and coarse tremor, and four days later experiened a grand mal seizure after which she was transferred for haemodialysis. Serum lithium levels on the preceding two days had been greater than 2 mEq/l. and 2·1 mEq/l. respectively. She was stuporous with frequent localized twitching of her face, upper and lower limbs, hyper-reflexia, and bilateral extensor plantar responses. A six-hour haemodialysis was performed using an Ultraflo 100 coil with access to the circulation via Seldinger catheters in the right groin.

The possibility of a significant rebound was recognized and in the presence of continuing coma, coarse tremor, and twitching muscles a further six-hour dialysis was carried out 24 hours later. After the second dialysis, which lowered the serum lithium to less than 0·6 mEq/l., the twitching diminished but the patient remained comatose for a further four days with increased tone, hyper-reflexia, and bilateral extensor plantar responses. An electroencephalogram, a skull *x*-ray picture, and a cerebrospinal fluid examinaton showed nothing abnormal. A transient fall in urinary output with a rise in plasma urea and creatinine to 80 mg/100 ml and 1·9 mg/100 ml was observed during the first two hospital days.

Six months later she remained very ataxic when walking on a wide base and needed the support of two people. She had choreiform movements involving head, tongue, and limbs with a compound rhythmic tremor affecting particularly the right hand. She had good muscle power, brisk reflexes, and bilateral extensor plantar responses.

Department of Medicine, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 4LP
B. VON HARTITZSCH, M.B., M.R.C.P., Senior Research Associate
N. A. HOENICH, M.SC., Scientific Officer
R. J. LEIGH, M.B., B.S., Senior House Officer
R. WILKINSON, M.B., M.R.C.S., Senior Lecturer in Medicine

University of Newcastle upon Tyne
T. H. FROST, B.SC.(TECH)., Lecturer in Mechanical Engineering

Newcastle General Hospital, Newcastle upon Tyne NE4 6BE
A. WEDDEL, B.SC., Biochemist

Ottawa General Hospital and University of Ottawa, Canada
G. A. POSEN, M.D., F.R.C.P., Consultant Physician

She had no nystagmus, and the only feature to suggest cerebellar involvement was inco-ordination in the heel-shin test.

Arterial and venous blood specimens were taken from the coil during dialysis of this patient for estimation of lithium clearance, then after dialysis from the Seldinger catheters to estimate the rebound. These lithium concentrations were analysed in batch on a Unicam Atomic SP 90 absorption spectrophotometer by A.W. (Pye Unicam Ltd., 1969).

Case 3

A 41-year-old woman was referred for dialysis after a routine plasma lithium of 3 mEq/1. She complained of no symptoms but was drowsy, with brisk reflexes and normal plantar responses. She was treated by peritoneal dialysis, which lowered the serum lithium level to 1·25 mEq/1. some 42 hours later. She had a low urine output of less than 400 ml/day during this period so renal excretion could have contributed very little to this fall. She made an uneventful recovery and had no lasting sequelae.

Results

Haemodialysis.—The lithium dialysance and calculated clearance data from case 2, shown in fig. 1 and table 1, indicate that lithium behaves not as a substance with molecular size compatible with its low molecular weight of seven but as a substance with larger molecular size. The probable explanation is

Lithium Clearance for Ultraflo 100 Coil

Blood flow (ml/min)	100	150	200	250
Lithium clearance (ml/min)	69	88	101	112

Clearance calculated by using: Clearance = $\frac{\text{Dialysance}}{1 + \frac{\text{Dialysance}}{\text{Dialysis fluid addition rate}}}$ (14).
Dialysis fluid addition rate 500 ml/min. Temperature 37°C.

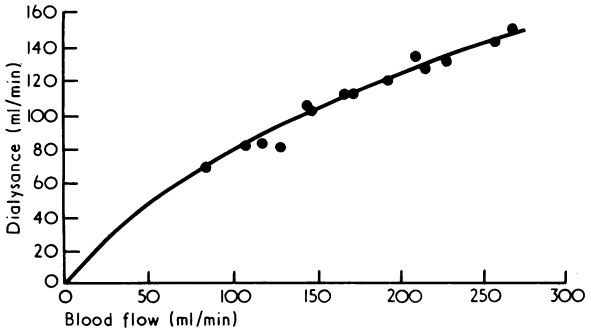

FIG. 1—Case 2. Lithium dialysance and clearance data with use of an Ultraflo 100 coil at 37°C.

that lithium with a rather active small nucleus attracts by covalent bonds a large hydration shell (A. K. Covington, personal communication; Robinson and Stokes, 1959) giving it a size and clearance similar to creatinine (99 ml/min at blood flow 200 ml/min) (von Hartitzsch *et al.*, 1972). A six-hour dialysis on an Ultraflow 100 coil resulted in a fall in serum lithium from 1·8 to 0·67 mEq/1., but a rise in serum levels to 1·2 mEq/1. within 10 hours occurred as lithium diffused or was extruded slowly from within the cells. The second six-hour dialysis reduced the level from 1·08 to 0·48 mEq/1. after which there was a 20% rebound to 0·62 mEq/1. compared with 40% after the first dialysis. Superimposed on these results in fig. 2 is the case described by Amdisen and Skjodborg (1969), which shows a 30% rebound after effective twin coil haemodialysis.

Peritoneal Dialysis.—In case 1, five cycles of peritoneal dialysis effectively lowered lithium levels from 5.0 to 2·5 mEq/1. in seven and a half hours. In case 3 the lithium level was reduced from 3-1·25 mEq/1. in 44 hours. The combined data

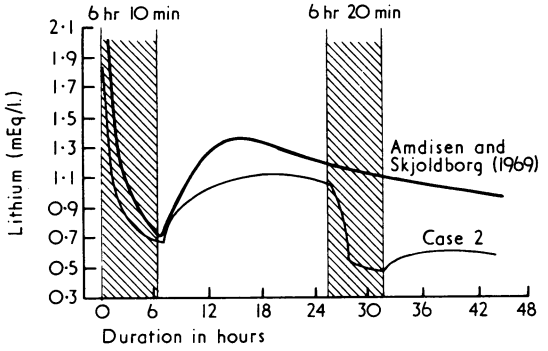

FIG. 2—Case 2. Serum lithium levels during and after haemodialysis compared with case of Amdisen and Skjoldborg, 1969.

suggest that peritoneal dialysis will lower toxic lithium levels but less rapidly than haemodialysis.

Discussion

Cases 1 and 2 show the features of lithium intoxication described by Schou *et al.* (1968). Prodromal symptoms of drowsiness, gastrointestinal disturbances, dysarthria, coarse tremor, and ataxia were followed by coma, coarse contractions of muscle, and epileptic seizure. Toxic serum lithium levels greater than 2 mEq/1. were present for four days in case 2 before the patient was referred for dialysis. The same appears likely in case 1, though no actual measurements are available until admission to hospital for dialysis.

Haemodialysis effectively lowered the serum levels but not before permanent neurological damage to basal ganglia and cerebellar connexions occurred resulting in lasting disabling choreoathetosis and ataxia. The similarity of presentation and lasting sequelae in these two cases exposed to toxic lithium levels for several days before the institution of active therapy is remarkable. Case 3, referred because a routine lithium level had been found to be 3 mEq/1., had minimal symptoms. The effective outcome is not related to the different forms of dialysis treatment, as haemodialysis is now a relatively safe procedure, and this type of problem has not been observed after actute poisonings of other types treated by haemodialysis. The different outcomes surely reflect the general condition of the patient at the time of presentation. In case 3 the patient was experiencing minimal symptoms, in cases 1 and 2 they were experiencing all the symptoms of severe lithium intoxication, and it is important to note that in case 2 these symptoms were present with relatively low levels.

Impaired renal function was also present as in previously described cases, but again it was not possible to be certain whether renal disease contributed to lithium toxicity or resulted from it—though the evidence favours the latter.

Conclusion

Permanent neurological damage can occur after exposure to toxic levels of lithium. The initial clinical state of the patient at the time of presentation seems to affect the outcome more than the initial serum lithium concentrztion. If these neurological sequelae are to be avoided physicians prescribing lithium-containing medications should be aware of the toxic manifestations and should obtain serum lithium levels immediately a patient shows any signs of drowsiness, nausea, vomiting, dysarthria, tremor, or ataxia. When toxic levels are confirmed prompt referral for dialysis is essential, since renal impairment is probably present either as a cause or as a consequence of lithium toxicity. Haemodialysis effectively removes lithium but the transfer between intracellular and extracellular compartments

is slow so that six to eight hours after a six-hour dialysis the effective lowering of the serum lithium is only 60-70% of that indicated by the postdialysis sample. This rebound can be prevented by longer duration haemodialysis (12-16 hours) (fig. 3) and possibly a further dialysis some hours later if the initial predialysis lithium levels are extremely high or further lithium is likely to be absorbed from slow-release lithium capsules in the alimentary tract. Where symptoms are less severe and facilities not available for haemodialysis peritoneal dialysis is effective in lowering lithium levels.

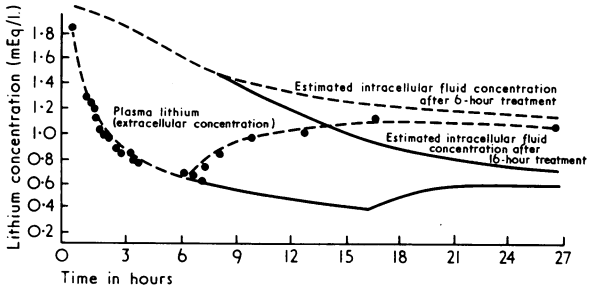

FIG. 3—Lithium removal by haemodialysis. Three pool model predictions when using data from case 2.

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Dyslexia as Cause of Psychiatric Disorder in Adults

W. A. SAUNDERS, M. G. BARKER

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Summary

A few patients may be of normal intelligence but have difficulties in reading, writing, and spelling, which are the main precipitants of a psychiatric disorder. In seven patients this illiteracy emerged only after intensive examination, as they had hidden it from employers, friends, and children. Characteristically these patients are often very sensitive about this disability and marital friction is common. They are also often noticeably resistant to remedial help.

Introduction

The World Federation of Neurology (1968) defined dyslexia as a disorder in children who, despite conventional classroom experience, fail to attain the language skills of reading, writing, and spelling commensurate with their intellectual abilities. Ingram (1964) and others emphasized the accompanying difficulties in writing spontaneously and spelling correctly. Various authors have described associated psychiatric disorders in childhood and adolescence, and these have been summarized by Critchley (1970) as non-specific and pleomorphic neurotic patterns.

This report deals with psychiatric disturbances in adults of normal intelligence who have hitherto unrecognized difficulties in reading, writing, and spelling, which appear causally related to their psychiatric disturbance and subsequent referral to a psychiatrist. A recognizable neurotic pattern is evident in these patients.

Barrow Hospital, Bristol
W. A. SAUNDERS, M.B., M.R.C.PSYCH., Registrar (Present appointment: Senior Registrar, Bristol Royal Hospital for Sick Children)
M. G. BARKER, F.R.C.P., M.R.C.PSYCH., Consultant Psychiatrist

Methods

All patients in this study were assessed by using the Weschler Adult Intelligence Scale (W.A.I.S.). Those subtests which are thought to depend heavily on educational attainments are separately scored (verbal score), and the other subtests which are thought to reflect the innate intellectual ability of the subject are grouped together under a different category (Performance Score). The combined results are given as Full Scale. Ravens' Matrices is a further test which gives an estimate of intelligence independent of verbal skills and educational background. The other attainment tests used were the Schonell Graded Word Reading Test (Reading Test), and the Schonell Graded Word Spelling Test A (Spelling Test). The remedial course referred to below was the *Audio-visual Programmed Reading Material* (Brown and Bookbinder, 1966).

Case 1

A 39-year-old married screensman was referred by his general practitioner with a six-month history of depression, agitation, and subsequent exacerbation of his asthma. He was found to have been depressed since promotion at work. At the end of a lengthy examination he disclosed that he was unable to read or write, a fact he had concealed from his employers over the years. After his promotion to foreman he had had to rely on his workmates to perform the paperwork now expected from him. He had become moody and irritable at work, argued with the foreman on the opposite shift, and was reprimanded by his employers because of these rows.

He had a stormy marital relationship and was described by his wife as moody, violent, and always ill at ease socially. She also reported that he was suspicious of her, and without any grounds suspected that she was interested in other men. Since his elder child started school and had been learning to read and write, his relations with his children had become strained. This became much worse when his seven-year-old child was awarded a gold star for reading at school.