Lithium neurotoxicity

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Summary

The peripheral and central neurotoxic effects of lithium carbonate are illustrated by 4 case histories. Lithium neurotoxicity is likely to be more common than the literature suggests. Neurological sequelae may be irreversible and may be associated with therapeutic serum levels. Prevention may be facilitated by more stringent case selection, EEG and clinical monitoring and the development of improved methods of drug level assessment.

Introduction

Lithium carbonate has been used in therapeutics for more than a century. The introduction of this drug to psychiatry (Cade, 1949) was overshadowed by the emergence of phenothiazine therapy, but it now has an established place in the treatment of manic depressive affective psychosis (Task Force, 1975). Despite regular drug monitoring, lithium therapy is frequently complicated by side effects and toxicity. Renal, endocrine, cardiovascular and gastro-intestinal side effects may occur but the most troublesome toxicity is seen with central nervous system involvement. Four cases of severe lithium neurotoxicity seen recently in a single neurology unit are reported to illustrate the various levels of the nervous system that may be affected and to emphasize that neurological morbidity from this drug is probably more widespread than has been thought. It is stressed that these 4 cases presented from an area where patients taking lithium are carefully monitored with frequent estimation of serum levels.

Case reports

Case 1

A 47-year-old industrial plant cleaner developed a manic illness in 1970. Neurological examination was normal and he made a good recovery with electroconvulsive therapy and a short course of lithium. In 1973 he relapsed and lithium was then given continuously until 1977. Two months after starting lithium he was found to have a spastic paraplegia with ataxia and mental deterioration. An

EEG showed diffuse delta activity, the spinal fluid contained 5×10^9 white cells/l and a protein level of 0.92 g/l. Myelography and air ventriculography were normal. The lithium level was then 0.7 mmol/l and ranged between 0.4 and 1.2 mmol/l until 1977 when he was re-admitted in a stuporous state. Neurological examination was otherwise unchanged. The lithium level was toxic at 2.3 mmol/l, the EEG showed frontal delta activity and the spinal fluid remained abnormal with 15×10^9 white cells/l and a protein of 1.16 g/l. Withdrawal of lithium resulted in a dramatic recovery from a bedridden and severely obtunded state, but he has remained moderately disabled by his ataxia and paraplegia. A trial of steroid therapy was unsuccessful following the emergence of further psychotic behaviour.

On clinical grounds the most probable cause of this neurological illness is multiple sclerosis but the highly active spinal fluid is distinctly unusual. Other conditions were looked for but detailed investigation was unhelpful. The onset of neurological disability was closely associated with the initiation of lithium treatment and hence the authors suspect that the clinical and biochemical aggressiveness of this presumed demyelinating lesion is linked with lithium.

Case 2

A 42-year-old housewife had been treated with lithium for several years because of a manic depressive illness. In 1976, 6 weeks before her admission, she complained of polyuria and polydipsia. She was initially manic but gradually became more withdrawn and then comatose. Neurological examination revealed flaccid paralysis of all 4 limbs, absent tendon reflexes and plantar responses. An EEG showed widespread high amplitude delta activity. The serum lithium level was 1.9 mmol/l several days after lithium had been discontinued. She was transferred to the Department of Neurology, Middlesbrough General Hospital, where her spinal fluid was found to be normal and where one month after her original admission she gradually regained consciousness. It was then found that she had a profound

muscular weakness, most marked proximally. Electromyography (EMG) showed widespread fibrillation in both proximal and distal muscle groups and the interference pattern was virtually absent. Motor and sensory nerve conductions were moderately impaired, suggesting an axonal neuropathy. Repeat EMG and conduction studies showed progressive improvement which was matched by a clinical return to normality over 6 months. The EEG remains abnormal with a slow dominant rhythm at 7–8 cycles per second (c/s) and a general excess of theta activity.

In this patient, a toxic lithium level was associated with coma, abnormal EEG and a widespread neuropathic process. Full recovery followed cessation of lithium treatment but a further episode of mania has subsequently intervened.

Case 3

A 62-year-old housewife was admitted in May 1978, disorientated and profoundly retarded. She had been on lithium for 7 months following the failure of tricyclics and phenothiazines to control relapsing depression, mania and confusional episodes, but this had been stopped several days before evaluation. Lithium levels had ranged from 0.65–1.1 mmol/l. Neurological examination demonstrated a mild spastic tetraparesis, generalized brisk reflexes, extensor plantar responses, bilateral palmar-mental reflexes and ataxia. The EEG was abnormal with widespread theta activity at 5–7 c/s and bilateral runs of delta activity. All other investigations including spinal fluid examination were normal. She made a spontaneous recovery with resolution of her ataxia, paresis and primitive reflexes but has subsequently relapsed with further retardation and confusion.

This patient developed an organic brain syndrome during treatment with lithium. Considerable improvement of her physical state and partial resolution of the abnormal mental state followed cessation of treatment. Interpretation of the role of lithium in this illness is difficult, as in so many cases of lithium neurotoxicity, but the conclusion is that lithium is implicated.

Case 4

A 44-year-old gardener was treated with lithium because of recurrent mania. Examination in April 1978 showed brisk reflexes and a bilateral intention tremor. In May he had a succession of grand mal convulsions, was acutely confused, visually hallucinated, confabulating and perseverating. In addition to the above findings he was dysarthric and exhibited marked asterixis, more left than right. The serum lithium level was 1.65 mmol/l. The EEG was abnormal with bitemporal theta and delta activity. Repeat EEGs showed some improvement but

remained abnormal. All other investigations were unhelpful and the patient steadily improved when lithium was stopped.

This patient developed epileptic fits and an acute confusional state associated with toxic lithium levels. There was a vague history of several fits more than a decade previously. There was no suggestion of alcoholic or other metabolic aetiology. Asterixis can theoretically occur in any toxic metabolic state but does not appear to have been observed before in lithium toxicity.

Discussion

These 4 cases of severe lithium neurotoxicity have been seen within a relatively short period of time in one unit. A recent survey of the reported cases of severe neurotoxicity mentioned only 38 cases (Strayhorn and Nash, 1977). This experience suggests that the true frequency may be much higher than suspected and that many cases may pass undetected.

Lithium toxicity is usually classified as (i) mild – fine tremor, weakness and lethargy, (ii) moderate – muscle fasciculation, ataxia, coarse tremor, dysarthria, inco-ordination, extrapyramidal syndromes, visual disturbances, confusional state, impaired consciousness, (iii) severe – progression of any of the above to coma, seizures, muscular flaccidity, marked cerebellar syndromes, irreversible brain damage and even death (Vacaflor, 1975; Jefferson and Greist, 1977). Significant neurotoxicity has appeared with normal serum levels (Strayhorn and Nash, 1977) and the elderly and schizophrenics are particularly liable to side effects (Shopsin, Johnson and Gershon, 1970). Neurological disability in mild and moderate toxicity is usually readily reversible but severe neurotoxicity may be irreversible (Goldwater and Pollock, 1976).

The first case above suggests that underlying neurological disorders may be precipitated and exacerbated by lithium therapy for incidental psychotic disturbances and this has been previously observed in a case of myasthenia (Neil, Himmelhock and Licata, 1976). Although a patient with multiple sclerosis complicated by a manic illness was successfully treated with a short course of lithium (Kemp, Lion and Magram, 1977), the present authors feel that lithium should be used with the utmost caution where psychotic illness is complicated by organic neurological disturbance, and only if other control measures have been unsuccessful. Red cell lithium levels may prove a more reliable indicator of incipient toxicity than the currently available serum levels (Hewick and Murray, 1976) and a series of therapeutic serum levels should not invite complacency. Intercurrent illness, impairment of renal function or concomitant diuretic therapy may precipitate toxicity in susceptible individuals.

Early detection of toxicity would be assisted by serial EEG monitoring of patients on lithium and perhaps by more frequent and more detailed clinical examination with urgent reassessment in the event of any abnormality being found.

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