PATHOLOGICAL NEUROTOXICITY WITH LITHIUM

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Introduction

Though lithium-induced neurotoxicity usually occurs when serum lithium exceeds 2.0 mEq/l, reports document its occurrence with serum lithium within the therapeutic range (Strayhorn and Nash 1977, Hansen and Amidsen, 1978, Speirs and Hirsch 1978, West and Meltzer 1979). Neurotoxicity has even been described with serum lithium between 0.4 and 0.5 mEq/l (Hansen and Amidsen 1978). Such may best be conceptualized as pathological neurotoxicity, in the sense that the expected side effect is obtained at a far lower dose or level than is usual. Many hypotheses have been suggested to explain this pathological neurotoxicity. These include: interactions with other drugs such as haloperidol and diuretics (Strayhorn and Nash 1977), diphenylhydantoin (Speirs and Hirsch 1978) and phenothiazines (Spring 1979), tissue retention and seizure diathesis (Strayhorn and Nash 1977), high pretotoxic global ratings of psychotic symptomatology and anxiety (West and Meltzer 1979), old age (Van der Velde 1971), Schizophrenia (Shopsin and Gershon 1973) and intercurrent medical illness (Shopsin and Gershon 1973, Strayhorn and Nash 1977).

Persistence of neurological deficits after recovery is also known, but not following pathological neurotoxicity (Hansen and Amidsen 1978, Schou 1984). Cerebellar deficits are most common, but pyramidal signs or cognitive deficits may also occur (Schou, 1984).

We present the course and outcome of a case of lithium-induced pathological neurotoxicity, discuss certain unusual features, and suggest a hypothesis to explain our observations.

Case Report

R., a 20 year old female, moderately mentally-retarded as per the diagnosis at a previous consultation, was brought with a 4 month history of psychological dysfunction fulfilling the criteria for a diagnosis of mania on DSM III. Physical examination was normal. She was started on lithium carbonate, 300 mg thrice daily. Eight days later, no abatement in mania was observed, but bilateral, horizontal, fixation nystagmus appeared. No other deficits were seen. Over the next 4 days, drowsiness, confusion and disorientation supervened; manic features were no longer seen. Besides nystagmus, the following cerebellar signs appeared bilaterally: dysdiadochokinesis, impaired heel to toe and finger-nose coordination, and gait ataxia. Bilateral pyramidal signs, more marked on the right side, were also present: spasticity, exaggerated tendon reflexes, ankle and patellar clonus and upgoing plantars. Fundoscopic examination was normal.

Lithium was immediately stopped and R. was extensively investigated. Serum lithium was 0.5 mEq/l. Haemogram, urinalysis, liver function tests, CSF analysis,

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ECG, chest and skull X-Rays and CT scan were all normal. EEG revealed slowing of background alpha to 7-8 Hz., seen diffusely and with bilateral symmetry.

Within 6 days of discontinuing lithium, the confusion, cerebellar signs and pyramidal signs remitted and the manic picture reappeared. Nystagmus, however, persisted. R. was administered 10 mg of haloperidol daily, and was discharged euthymic, 2 months later. Barring persistent nystagmus, physical examination was normal at discharge.

**Discussion**

This case presents several unusual features: a) neurotoxicity developed despite a serum lithium level of just 0.5 mEq/l. Literature describes just two cases where such pathological neurotoxicity has occurred at lower serum lithium levels (Hansen and Amidsen 1978), b) cerebellar signs were present early in the acute phase - in fact, nystagmus was the first neurological sign to appear. This contrasts with the observation of Schou (1984) that the acute phase of lithium neurotoxicity is without cerebellar symptoms; c) a long-term neurological deficit (nystagmus) resulted. This conforms with Schou's (1984) observation that persistent lithium-induced neurological sequelae (defined as those present more than 2 months after acute intoxication) are most commonly cerebellar in locus, but is unusual in that it occurred at a serum lithium level of 0.5 mEq/l. Schou's extensive review does not describe any case where lithium-induced neurotoxic sequelae obtained at serum lithium levels below 1.2 mEq/l.

Cases such as ours where intoxication (in the form of confusion with bilateral cerebellar and pyramidal signs, the latter suggestive of lateralization) occurs at a low serum lithium level, present the clinician with a diagnostic dilemma. Invariably the patient needs to be investigated extensively for possible intracranial pathology, and secondary mania has to be kept in mind. The diagnosis is established only after all investigations draw a blank and the clinical picture normalizes with discontinuation of lithium. It has been suggested that diffuse slowing of the EEG (as in our case) may be of great, perhaps diagnostic, significance at such times (Spring 1979).

Among the hypotheses proposed to explain lithium-induced pathological neurotoxicity are the following: seizure diathesis (Strayhorn and Nash 1977), increased age (Van der Velde 1971) and schizophrenia (Shopin and Gershon 1973). A common theme in these is an increased incidence of underlying demonstrable cerebral pathology. In this context, subclinical cerebral impairment has been proposed to be a predisposing factor for lithium-induced neurotoxicity. (Speirs and Hirsch 1978, Ghadirian and Lehmann 1980). Interestingly, a similar hypothesis has been proposed for the development of lithium carbamazepine neurotoxicity with the levels of both drugs being within the therapeutic range (Shukla et al 1984). Cerebral impairment was undeniable present in our case, since R. was moderately mentally retarded.

Individuals with brain damage may be more vulnerable to lithium-induced neurotoxicity (and possibly to the subsequent persistence of deficits) even at therapeutic serum lithium levels. Lithium should therefore be used with caution in such cases. The risk of pathological neurotoxicity may also warrant routine close supervision of lithium therapy, especially when treatment is being initiated.

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