Short report

A Creutzfeldt-Jakob like syndrome due to lithium toxicity

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SUMMARY Two patients with lithium toxicity presented with a neurological syndrome suggesting a diagnosis of Creutzfeldt-Jakob disease. In both cases, the initial EEG was consistent with this diagnosis. Neither patient had permanent neurological sequelae and the EEG returned to normal. A careful drug history should be taken in any patient who presents with a rapidly progressive dementia even when the EEG supports a diagnosis of Creutzfeldt-Jakob disease.

Lithium carbonate, a well established treatment for mania and recurrent affective disorders, has a variety of side effects. In patients on maintenance treatment with lithium, the relatively minor neurological side effects of tremor and rigidity of cogwheel type are common and rarely necessitate change in therapy. Acute intoxication with lithium in contrast can produce severe neurotoxicity with effects on both central and peripheral nervous systems. Patients may present with hypokinesia, rigidity, mutism, muscular twitches, coma and convulsions. An extrapyramidal syndrome resembling a severe Parkinsonian state, action myoclonus, cerebellar syndrome with myopathy, status epilepticus and acute generalised neuropathy have been described. In most cases the neurotoxicity is reversible, but permanent neurological sequelae of lithium toxicity may occur.

Lithium crosses the blood-brain barrier to enter brain tissue and can produce changes in the EEG of control subjects and patients with manic depressive disorders to whom lithium is given chronically. Acute administration, such as a single dose of 750 mg, does not alter the EEG. The changes in the EEG include disorganisation of background rhythms with widespread slow activity, usually of high amplitude, and superimposed fast rhythms. Lithium enhances sharp waves and spikes in epileptic patients and can induce epileptiform activity and seizures in patients with no previous history of epilepsy. The degree of EEG abnormality is partly dependent on the dose of lithium, changes occurring at serum levels of or greater than 1-2 mmol/l, and with intoxication, the EEG is most abnormal in the severely intoxicated and correlates with the degree of neurotoxicity.

Periodic-like complexes have not been described previously in the EEG of patients with lithium intoxication. We report two patients with a rapidly progressive dementia in whom the EEG showed periodic complexes suggesting a diagnosis of Creutzfeldt-Jakob encephalopathy, as did the clinical picture.

Case histories

Case 1 A woman aged 72 years had recurrent depression for 32 years treated with lithium carbonate 250 mg tds, with satisfactory serum levels. In 1980, she presented with a ‘trotty’ gait and tremor in her right arm. Mild Parkinsonism was diagnosed and she was treated with benzhexol hydrochloride and Madopar (levodopa/benserazide). Two months later, she became confused and withdrawn. She deteriorated over the ensuing few weeks, becoming bed bound, mute and incontinent with coarse tremor in both arms. On examination she was disoriented, emotionally labile and able to cooperate with only simple commands. She had tremor and cogwheel rigidity in the arms with relatively normal power.
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There was generalised hyperreflexia, bilaterally extensor plantar response and bilateral grasp reflexes.

Investigations showed normal haematology and biochemistry, except for a blood urea of 9-1 mmol/l. A CT scan showed mild cerebral atrophy. The serum lithium level was 1-2 mmol/l (therapeutic range 0-8-1-2 mmol/l). Her EEG showed a slow dominant rhythm of 4-6 Hz, with fast rhythms (12-16 Hz) and runs of periodic sharp waves, some with a triphasic outline, at 1-5-2 Hz. There were occasional episodes of high amplitude delta waves (see fig).

All treatment (lithium, promethazine, chlorpheniramine, indomethacin and Madopar) was stopped. Over the next 3 weeks her mental state improved, and she could walk unaided. Two further EEG recordings were obtained. The second, recorded 5 days after admission, showed reduction in slow activity and less evident sharp waves. Ten days later normal rhythms were present with occasional slow waves and no sharp waves.

Case 2 A woman aged 69 years with a history of depression for 40 years had been treated for 10 years with lithium carbonate 800 mg daily, blood levels being monitored regularly. One month before developing neurological symptoms she had an operation for knee replacement. In the next few days she vomited several times but had no diarrhoea. She became confused and deteriorated during the 2 weeks before admission. Her speech became monosyllabic and then incoherent, she was unable to stand or feed herself and she developed initially slight and then more severe involuntary myoclonic movements.

On examination, she was uncooperative, confused and only occasionally responding to simple commands. There were irregular twitching movements of the face and lips and myoclonic movements of the limbs at rest, more obvious when the limbs were passively moved, but not affected by sudden noise. Tone in the limbs was slightly increased, power and reflexes were normal, plantars were absent.

Routine haematology and biochemistry were normal except for an initially raised blood urea (14-5 mmol/l) and alkaline phosphatase (400 mmol/l). The CT scan was normal. The initial serum lithium level was 3-12 mmol/l. On treatment with parenteral fluids, the serum levels on the next successive days were 2-9, 2-0 and 0-8 mmol/l. On day three, the blood urea was 4-0 mmol/l. The first EEG showed widespread slow activity and runs of periodic sharp waves (1-2-5 Hz) which did not have a consistent waveform. The myoclonic jerks disappeared after 3 days and after a phase of perseveration and emotional lability, the mental state had returned to normal by 10 days. Three further EEGs recorded at 3, 7 and 15 days after admission, showed steady improvement with return of normal rhythms.

Discussion

The clinical features in the two cases which suggested a diagnosis of Creutzfeldt-Jakob disease were rapid.

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Fig Left: first EEG from case 1. Right: EEG of a patient with definite Creutzfeldt-Jakob disease (CJD) who was severely demented at the time of recording. Both records show loss of normal rhythms with widespread slow activity and periodic sharp waves. However, in the patient with lithium toxicity, the background is slower and more disorganised and in the patient with CJD, the periodic complexes occur with more consistent waveform and synchronicity.
onset of dementia with mutism, rigidity, primitive reflexes and in the second case, myoclonic jerks. This picture fits with the subacute variety of Creutzfeldt-Jakob disease, the most frequently encountered form of the disease. It has a course which is rapidly progressive from presentation, most commonly with deterioration in higher mental function and behaviour, to profound dementia and early death. The frequency with which various clinical symptoms and signs occurred in the subacute form of 158 cases of Creutzfeldt-Jakob disease described by Will and Matthews was dementia in 100%, myoclonus and muscular twitches in 82%, pyramidal signs in 79%, cerebellar signs in 42%, akinetic mutism in 39% and primitive reflexes in 30%. Extrapyramidal features were seen in only 3%, although patients with rigidity alone were classified as showing pyramidal signs.

Typical EEG changes of Creutzfeldt-Jakob disease are required for diagnosis of both definite and probable cases. Diffuse slowing of background activity and synchronous periodic complexes with an interval of 0.5-2 seconds in the EEG of a patient with rapidly progressive dementia is almost diagnostic of Creutzfeldt-Jakob disease. However, there is an evolution of EEG changes as the disease progresses which follows a similar pattern in the majority of cases. In the prodrome, when most patients have mild dementia only, normal background rhythms are preserved. When the disease is fully developed, background rhythms are replaced by diffuse theta and delta activity, often of high amplitude, and periodic sharp wave complexes appear. The diffuse slow activity may be a very early feature. In the terminal stage, the background becomes flat and the periodic complexes disappear. Although the periodic complexes tend to be seen in the fully developed stage of the disease, they may appear in the prodrome, even within 2 weeks of onset of symptoms. A variety of EEG abnormalities, therefore, may be seen at almost any stage of this disease, and although the EEGs of our patients with lithium neurotoxicity do not resemble the typical EEG of its terminal stage, the records from both patients were reported by experienced electroencephalographers as being very suggestive in the clinical context of Creutzfeldt-Jakob disease.

The pathogenesis of the periodic complexes in Creutzfeldt-Jakob disease is unknown. Recently, an attractive hypothesis proposed that spongiform degeneration causes fusion of neural processes producing abnormal electrotonic coupling between cells, so that large neuronal aggregates discharge synchronously. The repetition rate of periodic complexes may be determined by a refractory interval that is an intrinsic property of the membrane, perhaps the hyperpolarising calcium dependent K⁺ potential. How lithium produces neurotoxicity or electroencephalographic changes is also unknown. Cell membranes are equally permeable to lithium and sodium, and lithium activates the Na⁺/K⁺ ATPase pump, which however, may be inhibited in high concentrations. Lithium also affects the intra/extra cellular balance of other cations such as calcium and thus could alter intrinsic membrane potentials as neural fusion may do.

Periodic sharp waves are seen in many other conditions such as post-anoxic encephalopathy, head injury and cerebral infarction. To our knowledge, they have not been described in the EEG of patients who are intoxicated with lithium. Although neither patient had haemodialysis, as recommended for the treatment of acute lithium intoxication, both recovered satisfactorily over a period of 2 to 3 weeks with no permanent neurological damage. We suggest that in addition to the neurotoxic effects of lithium already described, acute intoxication may cause a syndrome which resembles Creutzfeldt-Jakob disease. That the deteriorating process in both patients was due to a metabolic rather than subacute spongiform encephalopathy was evident when serial EEGs were obtained. There was a reduction in slow activity with loss of periodic sharp waves and resumption of normal rhythms over 3 to 4 weeks in both cases. This is in contrast to what would be expected in Creutzfeldt-Jakob disease and emphasises the importance of obtaining serial records in both conditions, the EEG being one of the best means of monitoring a metabolic encephalopathy and the only noninvasive investigation of value in Creutzfeldt-Jakob disease.

References

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