
Reversible Creutzfeldt-Jakob like syndrome induced by lithium plus levodopa treatment

Sir: A clinical and EEG reversible syndrome due to lithium toxicity that resembles Creutzfeldt-Jakob disease has recently been described in the Journal. Although the authors claim that their two cases constitute the first report in the English literature, we would like to describe a personal observation that we published in 1972 in a French medical journal.

The patient was a 70 year old female who was admitted at the Department of Neurology in April 1971 with a Parkinsonian syndrome. She had experienced for 2 years resting tremor and dysarthria. Neurological examination, while the patient was under no medication, revealed akinesia, rigidity, tremor prominent in the left lower limb, bradyphrenia and mild memory impairment. The first EEG record showed intermittent slow activity of 2–3 Hz (fig). Routine haematology and biochemistry tests, including thyroid function, were normal.

Since the patient presented with an atypical parkinsonism with depression, levodopa plus lithium therapy was started. On the 10th day after admission, levodopa (without dopa decarboxylase inhibitor) was introduced progressively, reaching a daily dose of 2 g within 6 days. Lithium gluconate at a daily dose of 12 g was added 13 days after admission. On the 19th day, the patient became confused and agitated, and treatment was stopped. Nonetheless she worsened during the next 48 hours, presenting with a precomatose state, mutism, rigidity, sporadic myoclonic jerks that were prominent in the lower limbs, and urinary incontinency. The second EEG at that time was dramatically different from the first one (see fig), with increased theta activity of 5 Hz, and delta activity, predominantly in the frontal fields. Moreover there were triphasic waves and sharp waves particularly in the frontal fields, that were not synchronised with the concomittent myoclonic jerks of the upper limbs. Five mg diazepam IV suppressed for 4 min the sharp waves. Plasma sodium and ammonium levels were normal.

The patient improved on the fifth day after drug withdrawal. She had a normal consciousness, could feed herself and control her sphincters, was rather hypotonic and had no longer myoclonic jerks. Plasma lithium level was low (0.28 mmol/l). Nineteen days after discontinuation of treatment, the patient had only intermittent and mild confusion and no rigidity and tremor were observed. The last EEG was similar to the first one, with only intermittent slowing of activity.

Undoubtedly this patient experienced a reversible syndrome secondary to lithium and/or levodopa treatment, that is similar to the two case histories of Smith and Kocen. The lithium toxicity was secondary to the high dosage we prescribed (12 g daily of lithium gluconate). However, lithium therapy was still at an experimental stage in 1971. Further pharmacological studies showed that daily dosages must not exceed 4 to 6 g/day of lithium gluconate. Subsequently we have routinely used lithium therapy for mood disorders and we never observed again such a severe lithium intoxication. The clinical and EEG features of this peculiar syndrome of rapid onset include dementia, myoclonic jerks, rigidity, diffuse slowing of EEG activity with synchronous periodic complexes. It closely resembles that observed in Creutzfeldt Jakob disease. Levodopa and lithium toxicity appear to be the final diagnosis since laboratory tests eliminated a metabolic encephalopathy and most if not all signs disappeared after drug withdrawal.

Lithium may produce severe neurotoxicity, and most of the clinical and EEG signs (except periodic sharp waves) of the above-mentioned case histories have already been described, as reviewed by Smith and Kocen, and Dufour and Chazot. Similarly it has been reported for a long time that levodopa may be responsible for confusion. EEG changes, and even convulsions. It is likely that levodopa enhanced lithium toxicity in the two of three cases where both drugs were administered. The presence of atypical or mild Parkinsonism in our patient and in case 1 of Smith and Kocen also may have contributed to the occurrence of this severe neurotoxic syndrome.

The present case history and that of Smith and Kocen illustrates the fact that periodic sharp waves may be detected by serial EEG recordings, not only in Creutzfeldt-Jakob disease and metabolic encephalopathies,
Matters arising

including hyperammonaemia and hyponatraemia, but also in iatrogenicencephalopathies such as those produced by lithium and/ or levodopa. Although some tentative hypothesis can be proposed, the pathogenesis of periodic complexes still remains unknown.

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Smith and Kocen reply:
We thank Drs Brousselle and Chazot for drawing our attention to the case of a Creutzfeldt-Jakob syndrome due to lithium and levodopa toxicity, first reported in 1972. The case is very similar to those we described, although the clinical features appeared rather sooner after the first administration of lithium than in our two patients, who developed clinical features after 1 and 2 months. The dose of lithium used by Broussolle et al however was much higher. A further case of this syndrome has recently been identified (personal communication, Dr K Chiappa).

References
4. McPherson A. Convulsive seizures and dementia should not be uncritically applied to both. Ischaemic scores are of no use in excluding Alzheimer’s disease, nor are they helpful in differentiating so called mixed cases from vascular dementia. There is a 30% incidence of normal CTs in mixed or vascular dementias, and low densities in the periventricular white matter, characteristic of Binswanger’s disease, are also present in 10% of non-demented 55 to 70 year olds and 33% of patients with Alzheimer’s disease. Incidentally, if you like trendy new names as well as acronyms try “Leuko-araiosis” for the raffined white matter lesions.

The overall impression is that experts still apply disparate criteria for classification, study populations of different ages and with different aetiologies and employ different psychometric tests. Thus a unified picture fails to emerge. I particularly enjoyed reading Mirsen and Hachinski on epidemiology and classification, Philip Wolf and colleagues on epidemiology and prevention, Ross Russell on microvascular and macrovascular occlusions and Nicholls’ splendid review of Binswanger’s disease. Despite the rather forbidding subject matter, this is a useful compendium.

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Reversible Creutzfeldt-Jakob like syndrome induced by lithium plus levodopa treatment.
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J Neurol Neurosurg Psychiatry 1989 52: 686-687
doi: 10.1136/jnnp.52.5.686

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