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.1 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.2

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 glucurate 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 concomitant 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 glucurate). 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 glucurate. 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 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.3 Similarly it has been reported for a long time that levodopa may be responsible for confusion, EEG changes, and even convulsions.4 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 cases 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.

![Fig. EEG before treatment (A) and 48 hours after drug withdrawal (B). Note in A the intermittent delta activity and in B the triphasic waves, bilaterally, in the anterior fields, with diffuse sharp waves.](image-url)
Matters arising

including hyperammonaemia and hypokataemia, but also in iatrogenic encephalopathies 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 Brousséle and Chazot for drawing to our attention their 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 Brousséle et al however was much higher.

A further case of this syndrome has recently been identified (personal communication, Dr K Chiappa).

References

Book reviews


This is an excellent book. Iain Wilkinson has a high reputation for undergraduate teaching at Cambridge and this is reflected in his book. His priorities are clear as he has set out in the Preface. I also liked the way the book itself is set out. It is a pleasure to see illustrations that are related to text on the same page and are of good quality. I particularly liked the line illustrations and the diagrams are clear. It is good to see that common conditions are given appropriate prominence and detail whereas uncommon conditions such as myasthenia gravis are indicated as such. I have a number of quibbles, for example I cannot find ptosis listed in the main index but the Shy-Drager syndrome is. It would be better if eponyms were used less. I think it is a pity that the coma scale is introduced without the relevant numbers because the student cannot then grasp the significance of, say, a coma scale of 6 as opposed to a coma scale of 12. I have not come across the mnemonic A, E, I, O, U for coma before but its simplicity is obvious. It is a pity that the diagrams related to Parkinson’s disease did not make it clear that the striatum relays to the motor cortex and also that cerebellar damage results in changed inputs to the primary motor pathways.

However, overall this is an excellent book with a very good all round approach to an understanding of neurology at student level. I particularly liked his integration of counselling and genetic advice and I think this book will go a long way to dispel the myth that neurology is unduly complicated, a myth which tends to put off so many undergraduates.

Not least of all its attributes is the fact that its price is modest.

JE REES


This book is based on two seminars: one at Queens Square in December 1986, the other at Winston-Salem, N. Carolina in May 1987. Both were organised by the WFN Research Group on Cerebrovascular Disease. The topics under consideration are not the most promising areas for fruitful discussion nor areas for therapeutic euphoria; yet, the excellence of parts of this book will show otherwise. When you open it, your enthusiasm will not be enhanced by the cascade of dysphonious acronyms which assault the senses. I will not reproduce them, but if they are to be permitted at all, the editors might at least have adhered to one for the topic of the conference: not SDAT, DAT and AD in different sections.

The 26 chapters include a thorough coverage of clinical features, CT, PET and MRI scanning, electrophysiological tests as well as appraisal of sonography, haemorhology, biochemistry and a number of clinical drug trials. Some of the more general chapters present authoritative overviews, but they are too brief to be informative, and, though good introductions to leaven the heavy science at a symposium, might usefully have been omitted from the published work.

Progress may be hampered until fundamental issues of definition have been resolved, and it is clear they have not. No laboratory test or combination of clinical, psychometric and radiological criteria have been put forward to define dementia. Some feel dementia is not an all or none phenomenon, but a gradually developing entity; this approach beggars definition and if accepted would negate epidemiological studies and therapeutic trials. We are told that vascular lesions may not cause dementia; if they do, the cognitive impairment produced may differ qualitatively from that resulting from the parenchymal atrophy of Alzheimer’s disease. Some would argue for this qualification, but the distinction between 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 rarified 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 readings by Mirsen and Hachinski on epidemiology and classification, Philip Wolf and colleagues on epidemiology and prevention, Ross Russell on microvascular and macrovascular occlusions and Nichols’ splendid review of Binswanger’s disease. Despite the rather forbidding subject matter, this is a useful compilation.

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