Monza, Italy.
†*Division of Neurology, S. Gerardo Hospital, Monza, Italy.*
‡*Division of Neurophysiology, Niguarda-Cà Granda Hospital, Milan, Italy.*
§*Division of Anaesthesiology, Niguarda-Cà Granda Hospital, Milan, Italy.*

References

1 Taphoorn MJB, Van Duijn H, Wolters ECH. A neuromuscular transmission disorder: combined myasthenia gravis and Lambert-Eaton syndrome in one patient. *J Neurol Neurosurg Psychiatry* 1988;**51**:880–2.
2 Tabbaa MA, Leshner RT, Campbell WW. Malignant thymoma with dysautonomia and disordered neuromuscular transmission. *Arch Neurol* 1986;**43**:955–7.
3 Lennon VA, Lambert EH, Whittingham S, Fairbanks V. Autoimmunity in the Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1982;**5**:S21–S25.
4 Gutmann L, Crosby TW, Takamori M, Martin JD. The Lambert-Eaton syndrome and autoimmune disorders. *Am J Med* 1972;**53**: 354–6.
5 Castaigne P, Cambier J, Masson M, Cathala H-P, Pierrot-Deseilligny E. Le syndrome pseudo-myasthenique paraneopolasique de Lambert-Eaton. *Ann Med Int (Paris)* 1969;**120**:313–22.

Taphoorn et al reply:

We thank Ambrogio and colleagues for their comments on our paper.[1]

They describe a patient with features, as they argue, of both myasthenia gravis and Lambert Eaton myasthenic syndrome (LEMS). The neurophysiological data recorded are compatible with LEMS, as was so in our patient. The combination, however, of LEMS and myasthenia gravis in the patient reported on is less evident than in our patient and in several patients described in the literature, for no antibodies against acetylcholine receptors were detected in serum.[2-5]

The only features suggesting myasthenia gravis are the fluctuating oculobulbar symptoms, which are not exclusive for myasthenia gravis.[6] Moreover we doubt if the manner of death, explained by the authors as a myasthenic crisis, really adds to the diagnosis myasthenia gravis in this patient.

We do not believe the so called "overlap myasthenic syndrome" to be a separate clinical entity; it merely is a combination of the two auto-immune diseases (LEMS and myasthenia gravis) in one patient.

As to the therapeutic implications, patients with a combination of LEMS and myasthenia gravis may be treated with corticosteroids, effective in both diseases.[7,8] Our patient, on a 40 mg prednisone alternate day dose, is still in a good clinical condition.

References

1 Taphoorn MJB, van Duijn H, Wolters ECh. A neuromuscular transmission disorder: combined myasthenia gravis and Lambert Eaton syndrome in one patient. *J Neurol Neurosurg Psychiatry* 1988;**51**:880–2.
2 Fettel MR, Sin HS, Penn AS, Lovelace RE, Rowland LP. Combined Lambert Eaton syndrome and myasthenia gravis. *Neurology* 1978;**28**:398.
3 Singer P, Smith L, Ziegler DK, Festoff BW. Post-tetanic potentiation in a patient with myasthenia gravis. *Neurology* 1981;**31**: 1345–7.
4 Tabbaa MA, Leshner RT, Campbell WW. Malignant thymoma with dysautonomia and disordered neuromuscular transmission. *Arch Neurol* 1986;**43**:955–7.
5 Oh SJ, Dwyer DS, Bradley RJ. Overlap myasthenic syndrome: combined myasthenic gravis and Lambert Eaton syndrome. *Neurology* 1987;**37**:1411–4.
6 Kula RW. Facilitating myasthenic syndrome. In: Vinken PJ, Bruyn GW. *Handbook of Clinical Neurology*. Amsterdam: North Holland 1979;**41**:349–61.
7 Brunner NG, Namba T, Grob D. Corticosteroids in management of severe, generalized myasthenia gravis. *Neurology* 1972; **22**:603–10.
8 Streib EW, Rothner AD. Lambert Eaton myasthenic syndrome: long-term treatment of three patients with prednisone. *Ann Neurol* 1981;**10**:448–53.

Trial of ganglioside GM1 in acute stroke

Sir: In their therapeutic trial, recently reported in this Journal, Dr Hoffbrand and colleagues did not find GM1 therapy "to be of value in the treatment of acute stroke".[1] This indication seems in contrast with two previous clinical studies,[2,3] but the differences in the experimental designs, which are expression of two different approaches concerning the use of GM1 in stroke, may explain the discrepancies of the results.

In our trial[2] GM1 treatment was started two weeks after the onset of neurological deficits (when antioedema therapy had already been stopped) and it was continued daily for six weeks. At the end of this period the naturally occurring recovery after stroke was significantly enhanced by the drug. In our opinion GM1 seems to play a role in functional recovery by stimulating the adaptative reorganisation and the complex mechanisms of the neuronal plasticity (that is neuronal sprouting).

Hoffbrand and colleagues started GM1 therapy within 72 hours from the onset of the neurological deficits and continued for four weeks. It seems to us that such an approach might eventually show the antioedema effectiveness of GM1 (no other antioedema drugs were mentioned), but this drug effect has still to be demonstrated. Furthermore, this treatment could not clearly evaluate GM1 role in enhancing functional recovery because therapy was stopped too early.

Nevertheless, it must be pointed out that Hoffbrand's study reveals two data which are in partial accordance with our findings: (1) as regards mortality, the prognosis is better for patients on therapy with active drug: nine patients in placebo group and five patients in GM1 group died in Hoffbrand's trial, while in our study three patients in placebo and no one in GM1 group died (see patients and methods section of our paper); (2) in Hoffbrand's study, the mean increase in Barthel Index from the end of the first to the sixth month was 7·7 for the placebo group (from 72·3 to 80·0) and 18·0 for the GM1 group (from 70·2 to 88·2): probably such a wide difference is not statistically significant because the study group is not sufficiently large and homogeneous.

On the whole, these data indicate a possible effectiveness of GM1 in the treatment of stroke. We think that the real efficacy of the drug will be demonstrated not only by a larger study, but also through more selective criteria regarding the stroke (ischaemic or haemorrhagic) and the time of therapy (beginning and duration).

I APPOLLONIO
L FRATTOLA
M MASSAROTTI*
Neurological Clinic, University of Milan, San Gerardo Hospital, Monza, Italy.
**Fidia Research Laboratories, Abano Terme, Italy.*

Address correspondence to: Professor Frattola Lodovico, Clinica Neurologica, Ospedale San Gerardo, Via Donizetti, 106, 20052 Monza (MI), Italy.

References

1 Hoffbrand BJ, Bingley PJ, Oppenheimer SM, Sheldon CD. Trial of ganglioside GM1 in acute stroke. *J Neurol Neurosurg Psychiatry* 1988;**51**:1213–4.
2 Bassi S, Albizzati MG, Sbacchi M, Frattola L, Massarotti M. Double blind evaluation of

monosialonganglioside (GM1) therapy in stroke. *J Neurosci Res* 1984;12:493–8.
3 Battistin I, Cesari A, Galligioni F, *et al.* Effects of GM1 ganglioside in cerebrovascular disease: a double-blind trial in 40 cases. *Eur Neurol* 1985;24:493–8.

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.

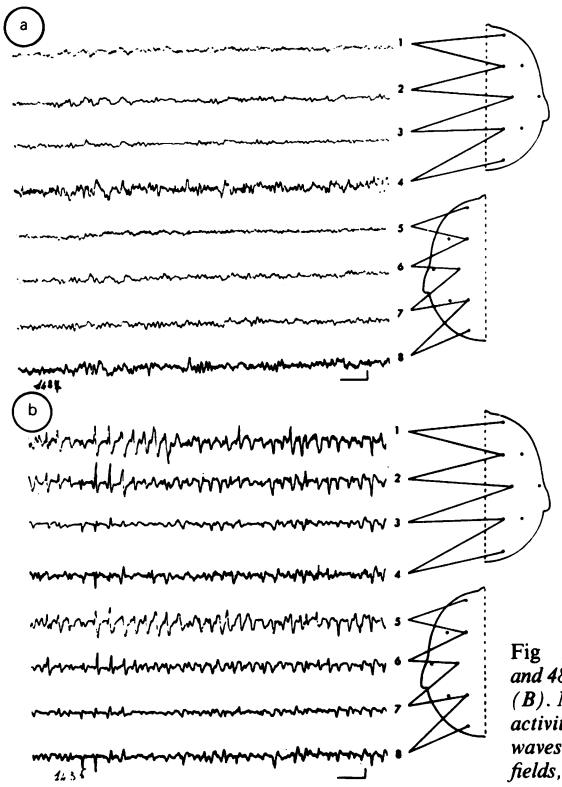

Fig *EEG before treatment (A) and 48 hours after drug withdrawal (B). Note in A the intermittent slow activity and in B the triphasic waves, bilaterally, in the anterior fields, with diffuse sharp waves.*

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.[1] 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.[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 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.