LETTERS TO THE EDITOR

A simple model to explain the motor fluctuations seen in Parkinson’s disease

Confusion and controversy surround the cause of motor fluctuations in Parkinson’s disease. Loss of dopamine storage capacity is the widely accepted explanation. The paper by Rodríguez et al has finally disproved this popular assumption. Motor responses for apomorphine and levodopa are identical. Apomorphine is not biotransformed to be active or stored in the brain excluding changes in the storage capacity as the explanation. Neither are there, in this study, any significant differences in the motor responses of new patients and patients treated with levodopa, eliminating any change in pharmacodynamics or phar-makinetikas as the explanation.

Fabbri et al and Bravi et al, however, have shown that the duration of motor response from “on” to “off” for levodopa and apomorphine respectively is shorter in patients with motor fluctuations. Because of this they have concluded that postjunctional mechanisms possibly due to treatment are responsible for the motor fluctuations in Parkinson’s disease.

I think that this conclusion is incorrect. I suggest an alternative explanation based on the following model, which satisfactorily explains the changes in motor performance with disease progression of Parkinson’s disease. The model shows that these changes are directly determined by the severity of the dopaminergic deficit, about which there is no disagreement. It requires no change in the pharmacology of the response to levodopa, no change in storage with disease progression and duration, and no postjunctional changes to explain the phenomena.

The figure represents two stages of Parkinson’s disease; early stable response and end of dose deterioration. It assumes a constant amplitude and duration of central dopaminergic stimulation due to a fixed dose of levodopa throughout the course of the disease. This is entirely dependent on the plasma concentration of levodopa with no storage of dopamine. A threshold of central dopaminergic stimulation for “on” is assumed as this corresponds to clinical experience. Variable amounts of motor response above this threshold are represented. This may be clinically apparent in some patients who get a better “on” with a larger dose; in others with early disease it may be “concealed” because the dose of levodopa is sufficient to achieve maximum “on”. The amount of central dopaminergic stimulation varies during this period of stable motor response due to the short plasma half life of levodopa, but because in early disease the amount of dopaminergic stimulation is always above threshold, wearing off is not apparent. The levodopa “dose response” curve remains constant throughout the course of the illness.

This model explains the observations of Fabbri et al, Kempster et al, and Rodríguez et al, and is able to reconcile them. It shows an increased amplitude of motor response with progression of disease. This is due to the greater difference between disability “on” and “off” with increasing disease duration.

There is no change in the total duration of motor response from “off” to “off”, which Kempster et al showed to be the case. It should be stressed that the duration of motor response measured in this instance is from “off” to “off” and not from “on” to “off”.

With disease progression and the development of motor fluctuations, there is faster wearing off from “on”. This is due to the differences in the amount of dopaminergic stimulation above the threshold. In early disease this is substantial and “concealed” so that no wearing off between doses is apparent, but with disease progression the amount of dopaminergic stimulation above the threshold is less so that wearing off of the response appears and occurs sooner in those patients with motor fluctuations. The rate of wearing off is changed, however. This agrees with the data of Bravi et al shown in fig 2 of their paper in which the slopes of the wearing off from uncomplicated patients, wearing off, and on-off fluctuators are identical. The model also explains the asymmetrical motor responses shown by Rodríguez et al. The latency to “on” is longer for the more affected side because more dopaminergic stimulation is required to reach “on” and the rate of increase of dopaminergic stimulation is identical for the two sides. The more severely affected side switches off sooner for the same reason that patients with motor fluctuations wear off before those with stable responses.

No change in post-synaptic receptor binding or other factors is required to explain the motor fluctuations that inevitably develop in Parkinson’s disease. They are an inevitable consequence of progression of the dopaminergic deficit and the short half life of levodopa. This model suggests therefore, that the duration of levodopa treatment is irrelevant to the development of motor fluctuations. This implies that withholding levodopa for as long as possible may deprive patients of a period of benefit without complications.


Severe intraventricular haemorrhage shown by computed tomography as an unusual manifestation of Wernicke’s encephalopathy

The most common pattern of presentation of acute Wernicke’s encephalopathy is an altered conscious state. The full clinical triad of Wernicke’s encephalopathy (ophthalmoplegia, ataxia, and abnormal mental state) is the exception rather than the rule (Harper et al, 1986, cited in Naidoo et al). We report on the case of a non-alcoholic patient with cancer who was shown to have Wernicke’s encephalopathy on necropsy. She died of massive intraventricular haemorrhage extending intraventricularly, a very uncommon manifestation of Wernicke’s encephalopathy.

A 59 year old non-alcoholic adipose woman was admitted to the University Hospital of Gynaecology in an acute, confused state that had developed over two days. She had had a vaginal hysterectomy three and a half years previously for cancer of the endometrium. A local recurrence of cancer six months later was treated with radiation therapy. Another tumour recurrence two years later required surgery followed by intermittent combination chemotherapy (epirubicine, carboplatin, and cyclophosphamide) for six months. Five weeks before admission recurrence of cancer was diagnosed. A low anterior resection of the rectosigmoid with colorectal anastomosis
mmol/l), total bilirubin (1.59 mg/dl), γ-glutamyl transferase (73 U/l), and prothrombin time (1.37 international normalised ratio, normal values from 1.00 to 1.27). Examination of CSF one day after admission showed a raised CSF/serum albumin ratio (12.5), but no neoplastic cells (or malignant cells were detected) and glucose concentration; fluid was sterile on culture. Oligoclonal IgG bands were absent in the CSF. A cranial CT on admission as well as bilateral carotid angiography three days after admission were normal. Five days after admission her mental state deteriorated. She was intubated and transferred to the neurology intensive care unit. On admission there she was comatose without reaction to painful stimuli. Oculocephalic responses were absent. The isocoric pupils had slight bilateral reaction to light. Corneal reflexes were symmetrically present. An ECG showed diffuse slowing. She had hypotension requiring fluid administration, dopamine, and noradrenaline. She had a fever (39°C) and a raised C-reactive protein concentration (13.8 mg/dl); antibiotic treatment (imipenem plus erythromycin) was initiated. Repeat cranial CT was normal. Twenty four hours after admission at the intensive care unit she acutely developed bilateral dilated pupils, bilateral Babinski, and were without reaction to painful stimuli. She was reported to have died of extensive haemorrhagic brainstem lesions detected on necropsy.

Wernicke's encephalopathy remains a clinical diagnosis, because of the sensitivity of neuroimaging in this setting. Initial CT in our patient was normal. Haemorrhages due to Wernicke's encephalopathy detected on CT or MRI are seldom reported; in one CT scan report scattered haemorrhages in the thalamus and posterior diencephalon in a patient with Wernicke-Korsakoff syndrome were shown by CT. In a case report a small haemorrhage in the midbrain was shown on MRI. The severe intraventricular haemorrhage due to Wernicke's encephalopathy as seen in our patient raises the question of whether spontaneous bleeding of Wernicke's encephalopathy was accentuated by an associated coagulopathy. At the time of ventricular haemorrhage the data on clotting studies were normal. Moreover, the patient had not received antiplatelet agents.

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Neuromyotonia in association with malignant hyperpyrexia

We report a case of neuromyotonia in a patient with malignant hyperpyrexia.

The patient, a 19 year old woman, had several discrete episodes of muscular stiffness over her head and neck and episodes of twitching in the hand and calf muscle. Episodes of calf muscle contractions and pain had occurred from the age of 5 with two severe episodes at the ages of 5 and 16.