Cognitive recovery instead of decline after acute encephalitis: a prospective follow up study

Laura Hokkanen, Jyrki Launes

Abstract

Objective—Follow up of cognitive sequelae of acute encephalitis and estimation of the frequency of persisting dementia.

Methods—Out of a series of 45 consecutive patients with acute encephalitis prospectively studied in 1990–95, 40 were screened for difficulty in everyday life using the Blessed dementia scale (BDS) 3.7 (1.4), mean (SD), years after onset. Eight patients had had herpes simplex encephalitis (HSVE), 16 some other identified aetiology, and in 21 the aetiology was unknown. All, except two patients with a non-herpetic encephalitis, were treated with acyclovir. All patients with disability in BDS (12/40), were invited to a neuropsychological reassessment, and the results of this assessment were compared with those of a similar assessment done after the acute stage. At follow up one patient could not complete the tests due to intractable epilepsy.

Results—In six of 11 cases the symptoms causing disability were mainly psychiatric. Five patients (two with HSVE) had a pronounced memory impairment together with other cognitive deficits, indicating dementia (frequency of 12.8%). In eight of the 11 testable cases cognitive performance had improved over the years, in two cases a decline was found and one patient with severe deficits showed no change. Intractable epilepsy was found in four of 12 cases.

Conclusion—Cognitive decline had taken place already at the acute stage, and further deterioration was uncommon. Considerable improvement occurred in most patients during follow up. Also in patients with HSVE treated with acyclovir the cognitive recovery was substantial and of a magnitude not expected based on previous literature. Intractable epilepsy contributed to the cognitive deterioration in some cases. Affective disorders also had a surprisingly important role for the long term outcome.

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Keywords: encephalitis; herpes simplex; cognitive performance; psychiatric sequelae

Encephalitides are known to cause severe cognitive decline in some patients. Among the acute encephalitides, Herpes simplex virus (HSV) has been the most commonly reported single aetiology leading to dementia.1–3 Untreated herpes simplex virus encephalitis (HSVE) is fatal in up to 70%, and results in severe deficits in 40%–60% of the survivors.4–7 Based on data published in the 1960s and 70s, the mortality in any encephalitis was 10%–50%, and 15%–28% of the survivors had neurological disability.8–10 In the 1980s antiviral medication, improvements in neuroimaging, and probably also other developments in the neurointensive care seem to have improved the prognosis. Today the mortality in patients with HSVE treated with acyclovir is 19%–28%, but 18%–42% of survivors are still reported of having severe deficits in follow up.10 11 Although the sequelae are mostly behavioural and cognitive, neuropsychological methods have not been systematically utilised. Cognitive deficits are often not detected in routine medical assessments. Even in cases with normal mental status examination, impairment has been found when a thorough neuropsychological assessment has been used.12

The damage caused by the herpes simplex virus to the CNS has been found to progress months after the acute stage in some cases untreated with antiviral medication.13 14 Also, relapses after a seemingly favourable recovery after antiviral treatment have been reported.15–17 Although this idea is not widely accepted,18–20 the presumably progressive nature of HSVE has generated the idea of HSV having a role in Alzheimer’s disease.21 22

To the best of our knowledge, no systematic follow up studies assessing the cognitive performance of a group of patients after acute encephalitides exist in the English literature. Previously we found that cognitive impairment initially occurs in 88% of the HSVE and in 56% of the non-HSVE encephalitic patients.23

We now aimed to study (1) does progressive deterioration really occur after acute encephalitis, or (2) do the cognitive deficits found in the acute stage later improve, and (3) how often acute encephalitides cause dementia?

Materials and methods

Patients

Forty five consecutive patients with acute encephalitis were prospectively studied between 1 January 1990 and 31 December 1994. The mean (SD) age of the patients was 40.8 (16.3) years (range 19 to 73), and the average length of the education was 11.0 (3.9) years. Twenty six of the patients were men, 19 women.

The diagnosis of encephalitis was based on clinical picture with symptoms and signs
suggested the involvement of brain parenchyma, EEG findings compatible with encephalitis, CSF findings compatible with infection of the CNS and CT excluding other intracranial causes. Standard laboratory tests were performed to exclude systemic disorders and generalised infections. Patients with alcohol misuse, and with coexisting or previous neurological disease were excluded. The microbial aetiology was verified in 24 (53%) patients. The diagnosis was established as described earlier. Eight patients had HSVE, seven had herpes zoster encephalitis, nine had some other specified aetiology, and in 21 cases the causative agent was unidentified.

Forty-three patients, including all patients with HSVE, were given intravenous acyclovir (30 mg/kg per day) for 11.0 (3.0) days. Acyclovir was started in 3.5 (4.5) days after the onset of first brain symptoms in all patients. In the patients with HSVE acyclovir was started within 24 hours in five, within two days in two, and within four days in one case. One patient was diagnosed as having epidemic nephropathy and one was strongly suspected of having tuberculous meningoencephalitis. These patients were treated accordingly and received no acyclovir. Ten patients had antiepileptic medication at discharge.

During follow up, EEG and standard laboratory tests were performed on all patients. Follow up CT or MRI was performed on 29 patients. Hospital records of neurological or psychiatric treatments during the follow up were also obtained.

ASSESSMENT OF DEMENTIA AND DISABILITY IN DAILY LIFE
To screen for patients with persisting disability, a questionnaire was sent to all patients in October 1995 (44.7 (16.3) months, after the onset of symptoms). The patients were asked about their current emotional, cognitive, and somatic complaints, as well as their employment status. A family member was asked to rate changes in the patient’s performance in everyday activities, and habits by employing the Blessed dementia scale (BDS). As well as the cognitive changes and activities of daily living, the BDS assesses personality and emotional changes, apathy, and withdrawal. This rating was used as the outcome measure in the follow up. In BDS higher points indicate a higher degree of disability. Four points or more of the maximum total of 28 was considered to indicate pronounced disability (unfavourable outcome), a rating of less than four points to indicate normal performance and favourable outcome. The questionnaire was returned in 40 of 45 cases (89%). According to the medical files, all five who did not reply had returned to gainful employment within a year after onset.

Dementia was diagnosed according to the DSM-III-R criteria. Pronounced memory impairment in combination with loss of other cognitive functions significantly interfering with social and occupational functioning was required. Memory impairment was considered substantial when the Wechsler memory quo-

Table 1. The neuropsychological test battery used in follow up, these 18 subtests were also used for calculating the test performance index.

<table>
<thead>
<tr>
<th>Intellectual functions:</th>
<th>1 WAIS information*</th>
<th>2 WAIS arithmetic*</th>
<th>3 WAIS vocabulary*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 WAIS digit symbols†</td>
<td>5 WAIS picture completion†</td>
<td>6 WAIS block design†</td>
</tr>
<tr>
<td>Memory:</td>
<td>7 WMS logical memory*</td>
<td>8 WMS associative learning</td>
<td>9 WMS visual reproduction</td>
</tr>
<tr>
<td></td>
<td>10 The Benton visual retention test†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language abilities:</td>
<td>11 Comprehension of sentences with complex semantic structures‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 Confrontation naming of pictures and body parts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscuapractic abilities:</td>
<td>13 Copy of a cube and a Greek cross</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 Clock hand task</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention and executive functions:</td>
<td>15 WMS mental control</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 The Stroop colour naming time*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 The Stroop colour-word interference time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 Word fluency: oral output of words beginning with a letter K in one minute (modification of FAS*)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For the estimation of the verbal IQ.
† For the estimation of the performance IQ.
‡ WAIS = The Wechsler adult intelligence scale; WMS = The Wechsler memory scale.

EVALUATION OF THE COGNITIVE DEFICTS
Neuropsychological appraisal
A thorough neuropsychological evaluation was first carried out at a mean of 26.5 (20.8) days (range 5–115) after the onset of symptoms, as soon as the patient could cooperate adequately. All patients with reported disability (the unfavourable outcome group) were invited to a neuropsychological re-examination, which was carried out using the same protocol as in the first investigation.

Table 1 shows the 18 neuropsychological subtests. The test battery was constructed following the guidelines for the assessment of dementia. One patient was assessed using a Luria based dementia battery (D-test) to avoid a floor effect due to a marked cognitive decline. The D-test includes subtests of orientation, memory and intellectual functions, as well as tasks of naming, semantic comprehension, and visuopractice and motor functions. Depression was assessed with the Beck depression inventory; scores above 17 were considered to suggest depression. The significance of the change in the patients’ performance during follow up was analysed using the non-parametric Wilcoxon matched pairs test. Also, we calculated a Test performance index (TPI) separately for both assessments. This was done by counting the number of subtests where the patient’s performance was within the normal range (maximum value 18 indicating intact performance).

Normative data
The normative data for the neuropsychological tests was obtained from a group of healthy controls (n=25) who were tested once. The control group, who initially had volunteered for a study of quantitative EEG at the Institute of
The unfavourable outcome group the frequency was 33%, which was significantly less (Fisher’s exact test $P<0.01$). There were four patients with intractable epilepsy in the unfavourable outcome group (33%) and only one in the favourable outcome group (3%) (Fisher’s exact test $P<0.05$). However, there was no difference in the number of patients having permanent antiepileptic medication in these groups (Fisher’s exact test).

**NEUROPSYCHOLOGICAL APPRAISAL**

The figure shows the TPI (the number of tests with normal performance) for the first and for the follow up assessment. In the selected group the neuropsychological re-evaluation was carried out at a mean of 36.6 (13.2) months after the onset (range 19–60). Patient 6 could not complete the test battery because of frequent epileptic seizures. An increase in the TPI was found in eight out of 11 re-examined cases. In one case (patient 10) there was no change and in two (patients 4 and 12) there was decrease in performance. The follow up assessment discovered pronounced memory impairment together with other cognitive deficits in five of the 11 patients (table 2).

Table 4 shows the group means of the 18 neuropsychological subtests initially and in the follow up. Case 6, who could not complete the tests, and case 12, who was assessed using a different test battery, are not included in this table. An increase in the mean performance was seen in 15 of the 18 subtests, and the improvement was statistically significant in WAIS digit symbols ($z=1.95$, $P<0.05$), Wechsler memory scale associative learning
Cognitive recovery after encephalitis

Table 4 The results of the first and follow up assessments in 10 of 12 patients with unfavourable outcome after encephalitis (one excluded patient was tested with a different test battery and another was unsuitable due to frequent epileptic seizures)

<table>
<thead>
<tr>
<th>Variable</th>
<th>First mean (SD)</th>
<th>Second mean (SD)</th>
<th>P value</th>
<th>Control mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information*</td>
<td>10.6 (3.5)</td>
<td>11.2 (3.0)</td>
<td>13.6 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Arithmetic*</td>
<td>10.0 (3.6)</td>
<td>10.3 (3.7)</td>
<td>12.5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Vocabulary*</td>
<td>10.5 (4.8)</td>
<td>12.0 (4.4)</td>
<td>13.7 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Digit symbols*</td>
<td>5.0 (3.8)</td>
<td>7.9 (4.7)</td>
<td>13.1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Picture completion*</td>
<td>10.0 (3.1)</td>
<td>10.6 (3.7)</td>
<td>12.2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Block design*</td>
<td>7.2 (4.3)</td>
<td>8.4 (5.7)</td>
<td>12.1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Logical memory†</td>
<td>6.4 (4.8)</td>
<td>7.8 (4.8)</td>
<td>12.7 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Visual reproduction†</td>
<td>4.0 (3.3)</td>
<td>7.5 (5.0)</td>
<td>11.7 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Associative learning†</td>
<td>9.0 (4.2)</td>
<td>13.9 (5.6)</td>
<td>18.7 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Benton VRT‡</td>
<td>5.0 (2.6)</td>
<td>4.9 (2.6)</td>
<td>8.0 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Sentence comprehension</td>
<td>9.8 (1.5)</td>
<td>9.6 (2.1)</td>
<td>10.8 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Naming</td>
<td>30.3 (7.3)</td>
<td>33.0 (3.2)</td>
<td>34.0 (0.2)</td>
<td></td>
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<tr>
<td>Copying</td>
<td>33.0 (6.3)</td>
<td>34.8 (8.2)</td>
<td>38.9 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Clock hands</td>
<td>21.7 (2.9)</td>
<td>22.0 (3.0)</td>
<td>23.8 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Mental control†</td>
<td>4.5 (2.9)</td>
<td>5.0 (2.5)</td>
<td>6.4 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Colour naming§</td>
<td>88.6 (22.8)</td>
<td>89.9 (56.1)</td>
<td>52.9 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Colour word naming§</td>
<td>226.5 (152.8)</td>
<td>217.0 (197.4)</td>
<td>94.4 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Word fluency</td>
<td>11.5 (4.5)</td>
<td>17.1 (8.4)</td>
<td>22.2 (4.9)</td>
<td></td>
</tr>
</tbody>
</table>

The significance of the difference in the patient means was tested with Wilcoxon matched pairs test. The means of the control group are given for comparison.

* The WASI, scaled score.
† The WMS.
‡ The Benton visual retention test, correct pictures.
§ The Stroop test, time in seconds.

(z=2.67, P<0.01), and verbal fluency (z=1.99, P<0.05). There was no statistically significant decrease in the mean performance in any of the subtests.

PSYCHIATRIC SEQUELAE

Eight patients had suffered from emotional instability or personality change during follow up (table 2). The psychotic symptoms included panic disorder and anxiety in patient 1, bipolar affective disorder with predominantly manic behaviour in patient 2, aggressive outbursts and irritability in patients 3 and 5, and depression in patients 7, 8, 9, and 11. Klüver-Bucy syndrome was not encountered.

Discussion

Psychometric testing alone is not adequate for diagnosis of dementia when the DSM-III-R criteria are used. Social competence and behaviour must also be assessed—for example, by using behavioural rating scales or questionnaires. The BDS rated by a family member has been validated for dementia screening. In the validation study the cut off point of 4 gave a sensitivity of 90% and specificity of 84% for dementia. The Blessed scale has been found to correlate with neuropathological changes and it has been used for measuring longitudinal changes in the functional capacity in dementia. However, it is less reliable in predicting the cognitive test performance because psychiatric symptoms are also included in the total score.

The accuracy of data gained by mailed questionnaires may be limited by a high drop out rate. In this study 89% returned the query, which is adequate for a reliable analysis. Furthermore, as the non-responders had previously reported to have returned to their previous employment, we think that we have found all demented patients in this series.

The 28 patients with favourable outcome included patients who initially had substantial cognitive deterioration (low TPI). Although they were not re-examined, it is likely that some neuropsychological deficits still persist in these patients. However, they were reported to be independent in everyday activities by their family members, and therefore they do not fill the DSM-III-R criteria for dementia. Young age may be a positive prognostic factor in encephalitis. The patients with favourable outcome were on average younger than the patients with unfavourable outcome.

Twelve out of 40 responders had difficulty in daily activities. At re-examination, five of them had persisting memory defect and other cognitive deficits. One patient in the unfavourable outcome group could not be re-tested due to frequent seizures. Thus the frequency of dementia was 12.8% among the re-tested responders, and 11% among the total sample of 45. The follow up time (about 3.7 years) is still relatively short, and possibly in the long run some of the patients will develop dementia. It has been suggested that patients with brain injury (or other lesions) may be more susceptible to the effects of aging. An association between remote brain injury (latencies up to 30 years) and Alzheimer’s disease has recently been found in a longitudinal incidence study. In single cases, however, it is extremely difficult to establish the causal relation between an earlier neurological disease and dementia appearing decades later.

The frequency of dementia after encephalitis does not seem to be higher than after stroke or brain trauma according to the literature. However, comparisons are difficult due to differences in the definitions of dementia and study protocols. In one cross sectional study with stroke patients the frequency of dementia was as high as 58% in patients having only one ischaemic event. On the other hand, in a four year longitudinal study the frequency of dementia after a single stroke was only 6%. In brain injury, the frequency of dementia according to one follow up study was 21%. Our figure of 12.8% falls within these boundaries. Also the trend in recovery is comparable with other patient groups. The performance in a single memory test followed up for 5–10 years after brain trauma showed no change in 58%, improved in 31%, and deteriorated in 11% of the patients. In our study the cognitive symptoms after encephalitis improved in eight of 11 (73%) patients. Two of the 11 patients (18%) deteriorated over the years, and one initially severely affected patient (9%) did not change.

Unfavourable outcome was not caused by cognitive decline only. Six of the 12 patients with unfavourable outcome had changes in personality and mood, which were severe enough to interfere with daily living. Three of the six performed within the normal range in almost all neuropsychological measures at re-examination, and were also employed in their previous occupation. Minor neuropsychological impairment was found in the three other cases, but mainly the problems were caused by the persisting mood change. These psychiatric symptoms can on the one hand be explained by an emotional reaction to a
possibly fatal illness, whereas on the other hand symptoms may also be due to damage to the limbic system caused by encephalitis. In particular HSVE is known to affect the limbic structures,40-42 resulting sometimes in severe changes in behaviour and personality, including the Klüver-Bucy syndrome.43-45 Affective disorders may also occur after herpes zoster46 and other viral encephalitides.47-50

Four patients in the unfavourable outcome group had intractable epilepsy. It may be argued that the frequent seizures contributed the most to the cognitive decline in these cases. It has been shown that high seizure frequency may have a detrimental effect on cognitive functioning.51-53 Memory performance especially may deteriorate because of epilepsy related neuron loss in the hippocampus.54 Epilepsy does not invariably lead to poor outcome, however. In our material one patient was rated independent in everyday activities despite frequent seizures. This young patient, as well as his family, agreed that apart from the ictal and postictal confusion, he performed normally.

In our series the cognitive outcome of patients with HSVE was more favourable than would be expected based on the literature.55 This may be due to starting acyclovir therapy within four days of the onset, which was made possible by the general awareness of encephalitis and the improvements in neuroradiological methods (MRI and CT). Two out of eight of our patients with HSVE were close to normal in the first neuropsychological assessment, and two recovered in follow up to be rated to perform normally in everyday situations. Four were re-examined because of reported difficulty in everyday life but only two were found to have persisting cognitive deficits. One of them had deteriorated during follow up. Altogether five (71%) of the seven patients with HSVE who initially were not retired, were eventually able to retain gainful employment. It has been argued that acyclovir treatment decreases the mortality but increases the relative frequency of cognitive deficits in surviving patients.54 Our findings suggest that this is not true.

In conclusion, after an average follow up of 3.7 years, the frequency of dementia was 12.8% in 40 consecutive patients with acute encephalitis. In most patients the cognitive decline had taken place already at the acute stage. The cognitive performance improved in all but three cases, two of whom had frequent seizures. Seventy seven per cent of employed patients had returned to their previous occupations.

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Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson’s disease

A Churchyard, C J Mathias, P Boonkongchuen, A J Lees

Abstract

Objectives—The United Kingdom Parkinson’s Disease Research Group (UKPDRG) trial found an increased mortality in patients with Parkinson’s disease randomised to receive selegiline (10 mg/day) and levodopa compared with those taking levodopa alone. Unwanted effects of selegiline on cardiovascular regulation have been investigated as a potential cause for the unexpected mortality finding of the UKPDRG trial.

Methods—The cardiovascular responses to a range of physiological stimuli, including standing and head up tilt, were studied in patients with Parkinson’s disease receiving levodopa alone and a matched group on levodopa and selegiline.

Results—Head up tilt caused selective and often severe orthostatic hypotension in nine of 16 patients taking selegiline and levodopa, but was without effect on nine patients receiving levodopa alone. Two patients taking selegiline lost consciousness with unrecordable blood pressures and a further four had severe symptomatic hypotension. The normal protective rises in heart rate and plasma noradrenaline were impaired. The abnormal response to head up tilt was reversed by discontinuation of selegiline. Drug withdrawal caused a pronounced deterioration in motor function in 13 of the 16 patients taking selegiline.

Conclusion—Therapy with selegiline and levodopa in combination may be associated with severe orthostatic hypotension not attributable to levodopa alone. Selegiline also has pronounced symptomatic motor effects in advanced Parkinson’s disease. The possibilities that these cardiovascular and motor findings might be due either to non-selective inhibition of monoamine oxidase or to amphetamine and met-amphetamine are discussed.

Keywords: Parkinson’s disease; selegiline; orthostatic hypotension

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Selegiline HCl (10 mg/day) selectively and irreversibly inhibits monoamine oxidase B (MAOB) and does not cause a “cheese effect” when taken with tyramine containing foodstuffs or levodopa. Blockade of MAOB inhibits its metabolism of dopamine and is thought to reduce production of free radicals as well as to increase cerebral dopamine. Selegiline protects against MPTP induced neurotoxicity, and was claimed following the initial publication of the DATATOP study to slow the rate of disease progression and to delay the need for levodopa (“neuroprotective effect”) in Parkinson’s disease. However, DATATOP assumed that the anti-parkinsonian effects of selegiline were negligible. The UKPDRG trial and longer follow up in the DATATOP study failed to show a functionally significant neuroprotective effect and confirmed the symptomatic benefits of selegiline. Moreover, selegiline combined with levodopa was associated with greater mortality than levodopa alone in the UKPDRG trial, although no single cause was identified and no definite causal relation with selegiline was proved.

Selegiline is metabolised to metamphetamine and amphetamine (-isomers) which increase synaptic release of catecholamines and deplete catecholamine stores in surviving terminals. Amphetamine is metabolised to the false neurotransmitter p-hydroxyephedrine, which also depletes nerve terminals of noradrenaline. Acute and subacute exposure of healthy humans to amphetamine results in a supine pressor response and postural hypotension and alters the pressor response to tyramine and noradrenaline, consistent with increased release of noradrenaline, depletion of noradrenaline in sympathetic terminals, and a false transmitter action of p-hydroxyephedrine. Selegiline inhibits noradrenaline uptake and release in the central and peripheral nervous systems in vitro and is a weak indirect sympathomimetic acting on the peripheral sympathetic nerves in the rat. We have studied the responses to a range of cardiovascular autonomic stimuli in patients with Parkinson’s disease receiving levodopa with or without selegiline to determine if autonomic dysfunction might be a relevant factor in explaining the increased mortality found in the UKPDRG study.

Patients and methods

Consecutive patients receiving oral levodopa with or without oral selegiline (10 mg/day) and satisfying the UKPDS Brain Bank clinical criteria for Parkinson’s disease were entered into the study after approval by the hospital ethics committee. The presence or absence of symptomatic autonomic dysfunction did not influence entry. Patients receiving only dopamine agonists or with Hoehn and Yahr stage IV and V disease or age over 75 years were excluded.
because of concern that their frailty would prevent adequate performance of the tests. Those living beyond metropolitan London were excluded because of the impossibility of attending before noon. All patients taking levodopa or levodopa and selegiline in our clinic seen in a four month period were approached and all entered and completed the study. At the first examination, patients completed a detailed questionnaire of the following symptoms of autonomic dysfunction: postural and postprandial dizziness/impairment of conscious state, impotence, urinary urgency, frequency and incontinence, diminished tolerance to extremes of temperature, Raynaud's phenomenon/cold extremities, abnormal sweating, constipation, dry eyes, or dry mouth. Those not receiving selegiline were tested once. Those on selegiline were tested once on the drug and three months after its withdrawal. The severity of parkinsonism was rated at each visit (Hoehn and Yahr, North Western University Disability Scale [NWUDS], Websters).

Subjects were studied in a dedicated autonomic function laboratory before noon after taking their normal breakfast and medications. After 20 minutes supine during which patients were familiarised with the equipment and their blood pressure and heart rate had stabilised, we were familiarised with the equipment and their heart rate had stabilised, autonomic testing using previously described techniques measured blood pressure and heart rate when supine at 20 minutes and with the following manoeuvres dependent on sympathetic function: head up tilt to 45° at two and 10 minutes and on standing at two minutes, the 30:15 ratio, the response to mental arithmetic for two minutes, application of a cold face pack for 45 seconds, and the cold pressor test for 40 seconds. Vagal function was assessed by the heart rate response to deep breathing for two minutes (R-R variation) and the Valsalva ratio (15 seconds; minimum pressure 20 mm Hg) examined the baroreflex, which is dependent on sympathetic and vagal function. Patients were continuously monitored with a three lead ECG. Blood pressure and heart rate were measured intermittently with a Critikon Dinamap 1846SX. The QT interval was measured manually from a 30 second ECG strip taken after 20 minutes supine so as to detect coincidental predisposition to any arrhythmias which might arise during the study. The humoral response to head up tilt, also dependent on the sympathetic system, was examined. A 16G venflon catheter was inserted before testing and 5 ml blood was taken after 20 minutes supine and 10 minutes tilting for plasma catecholamine concentrations. Samples were immediately mixed with 0.1 ml EGTA/reduced glutathione and stored on ice before centrifugation (3000 rpm for 10 minutes at 4°C). Plasma was pipetted off, immediately frozen, and stored before measurement of noradrenaline and adrenaline concentrations with high pressure liquid chromatography (HPLC) with electrochemical detection. Comparison between patient groups was with Student's t test and the significance of changes in each index induced by each challenge was assessed with one way analysis of variance (ANOVA) (Excel 4.0).

Results
Nine patients on levodopa (group I; three men, six women) and 16 patients taking 10 mg/day selegiline and levodopa (group II; nine men, seven women) were matched for age (group I: 69.6 (SEM 2.3) years; group II: 68 (SEM 1.1), disease duration (group I: 7.1 (SEM 0.8) years; group II: 9.6 (SEM 0.8)), disease severity, and daily levodopa dose (table 4). The mean duration of selegiline treatment was 6.4 (SEM 0.8) years. Single patients in each group were taking an ergolene, amantadine, or an anticholinergic or antidepressant drug. These drugs were not changed during the duration of the study. Five group I (56%) and seven group II (44%) patients were participating in the UKPDRG trial. There were no differences between these and the non-trial patients with respect to disease severity or duration, age, frequency of postural dizziness, or antiparkinsonian medication. Three patients (two in group I, one in group II) had treated hypertension. No patient had symptomatic coronary artery disease or risk factors for myocardial ischaemia. All complained of constipation and a dry mouth. Five group I (56%) and six group II (38%) patients reported postural dizziness in the questionnaire, but this was pronounced only in four group II patients. One group II patient had frequent orthostatic hypotensive transient ischaemic attacks suggesting impairment of posterior cerebral circulation (bilateral blindness, vertigo, dysarthria, and impaired consciousness) which developed shortly after he started selegiline; multiple bilateral posterior cerebral watershed infarcts were detected on MRI, but no vertebrobasilar or carotid stenoses were identified by MR angiography. Four group I (44%) and eight group II (50%) patients had urinary urgency and frequency consistent with detrusor instability. None of the patients had clinical or laboratory features of multiple system atrophy or autonomic failure.

No group I patient developed symptomatic hypotension with head up tilt (table 1, figure). By contrast, selegiline therapy was associated with severe and often symptomatic systolic hypotension on tilting (table 1, figure). In nine (56%) selegiline patients, systolic blood pressure fell by 20% or more after tilting for 10 minutes, whereas only two (22%) group I patients recorded a 20% drop (figure). Head up tilt caused loss of consciousness and postural dizziness in two patients on selegiline (figure), only one of whom had a history of postural dizziness. The other three patients with disabling symptomatic postural dizziness before the study were very hypotensive on tilting, although with only mild symptoms. Tilting caused considerable systolic hypotension with severe dizziness and impaired consciousness or cognition in a further four patients taking selegiline, none of whom had a history of postural dizziness. Therefore, five of the six patients with severe hypotension on tilting had
Table 1  Response of systolic and diastolic blood pressure (mm Hg), heart rate (beats per minute), and plasma catecholamines (pg/ml) (mean (SEM)) to head up tilting at 45° for two and 10 minutes

<table>
<thead>
<tr>
<th>Posture</th>
<th>Group I: levodopa only (n=9)</th>
<th>Group II: selegiline and levodopa (n=16)</th>
<th>Group II: selegiline ceased (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine systolic BP</td>
<td>143.3 (7.7)</td>
<td>141.6 (4.5)</td>
<td>134.6 (3.4)</td>
</tr>
<tr>
<td>Tilted systolic BP at 2 min</td>
<td>143.2 (10.6) (range 103 to 181)</td>
<td>123.3 (5.7) (range 73 to 136)</td>
<td>127.2 (6.7) (range 79 to 183)</td>
</tr>
<tr>
<td>Tilted systolic BP at 10 min</td>
<td>138.7 (10.6) (range 99 to 184)</td>
<td>116.3 (9.2) (range 0 to 175)</td>
<td>128.0 (4.4) (range 92 to 164)</td>
</tr>
<tr>
<td>Tilted diastolic BP at 2 min</td>
<td>87 (5.4)</td>
<td>82.9 (3.1)</td>
<td>77.6 (2.0)</td>
</tr>
<tr>
<td>Tilted diastolic BP at 10 min</td>
<td>84.1 (5.6) (range 64 to 115)</td>
<td>77.8 (3.6)</td>
<td>72.1 (2.6) (range 56 to 93)</td>
</tr>
<tr>
<td>% Change systolic BP at 2 min</td>
<td>−3.4 (1.8) (range −14 to 5)</td>
<td>−5.9 (3.6)</td>
<td>−6.9 (2.9) (range −3.3 to 10.7)</td>
</tr>
<tr>
<td>% Change diastolic BP at 10 min</td>
<td>86.6 (5.9) (range 57 to 115)</td>
<td>67.8 (8.1)</td>
<td>77.3 (3.4) (range 58 to 97)</td>
</tr>
<tr>
<td>% Change systolic BP at 10 min</td>
<td>−1.0 (2.8) (range −16 to 11)</td>
<td>−14.5 (9.6)</td>
<td>−0.3 (1.8) (range −12.1 to 11.5)</td>
</tr>
<tr>
<td>Supine HR</td>
<td>75.3 (3.6)</td>
<td>79 (2.5)</td>
<td>72.2 (1.9)</td>
</tr>
<tr>
<td>Tilted HR at 2 min</td>
<td>88.9 (5.4) (range 59–100)</td>
<td>87.3 (4.8) (range 65 to 129)</td>
<td>74.8 (2.0) (range 65 to 93)</td>
</tr>
<tr>
<td>Tilted HR at 10 min</td>
<td>76.9 (4.4) (range 54 to 96)</td>
<td>81.5 (3.8) (range 61 to 113)</td>
<td>75.8 (1.8) (range 63 to 92)</td>
</tr>
<tr>
<td>% Change HR at 10 min</td>
<td>2.1 (2.3) (range −10 to 13)</td>
<td>2.2 (2.3) (range −16 to 8)</td>
<td>5.2 (1.5) (range −3.1 to 16.7)</td>
</tr>
<tr>
<td>Lying noradrenaline (NA)</td>
<td>297.4 (35.0)</td>
<td>540.0 (209.4)</td>
<td>345.4 (58.1)</td>
</tr>
<tr>
<td>Tilted NA at 10 min</td>
<td>402.3 (55.4)</td>
<td>514.9 (106.9)</td>
<td>413.5 (62.1)</td>
</tr>
<tr>
<td>% Change HR at 10 min</td>
<td>−12.9 (6.3) (range −3 to 11)</td>
<td>−11.0 (5.6) (range −2 to 19)</td>
<td>−3.6 (1.4) (range −2.7 to 20)</td>
</tr>
<tr>
<td>% Change HR at 10 min</td>
<td>−21.9 (5.4) (range −73 to 136)</td>
<td>−12.2 (2.3) (range −79 to 183)</td>
<td>−5.2 (1.5) (range −3.3 to 10.7)</td>
</tr>
<tr>
<td>% Change HR at 10 min</td>
<td>−3.6 (1.4) (range −2.7 to 20)</td>
<td>−5.2 (1.5) (range −3.3 to 10.7)</td>
<td>−5.2 (1.5) (range −3.3 to 10.7)</td>
</tr>
</tbody>
</table>

As absolute and percentage changes were similar, only the percentage changes are shown. Selegiline therapy was associated with symptomatic hypotension after two and more markedly at 10 minutes of head up tilting. Withdrawal of selegiline resulted in resolution of hypotension induced by tilting. Diastolic blood pressure and heart rate were unaffected. Selegiline therapy was also associated with failure of the normal rise in plasma catecholamines. Comparison between group I and group II: P<0.05, paired t test. Comparison between group II patients before and after drug withdrawal: ‘P<0.05, paired t test.

Effects of lying, head up tilt at 45°, and standing on systolic blood pressure (supine: su, 2 minute tilt: t2, 10 minute tilt: t10, standing: st). Selegiline therapy was associated with orthostatic hypotension on tilting at 10 minutes and lesser hypotension on tilting for 2 minutes and standing. On tilting for 10 minutes, six patients on selegiline developed symptomatic hypotension and in five the blood pressure fell to below 100 mm Hg. Withdrawal of selegiline abolished symptomatic postural hypotension on tilting. The systolic blood pressure at tilting for 10 minutes fell below 100 mm Hg in only one previously severely hypotensive patient after selegiline was stopped and this fall was asymptomatic.

Standing at two minutes had no effect on blood pressure or heart rate in group I patients, but caused an asymptomatic fall in systolic and diastolic blood pressures accompanied by a rise in heart rate in group II patients which was abolished by stopping selegiline (table 2). No other abnormalities of autonomic function were detected (table 3). One patient taking selegiline had 8 beats of ventricular tachycardia (VT) during deep breathing, but a subsequent 24 hour ECG and echocardiograph were normal. Selegiline therapy was not associated with an increased QT interval, even in the patient with ventricular tachycardia (group I: 0.37 (SEM 0.01) s; group II: 0.36 (SEM 0.01) s on selegiline, and 0.38 (SEM 0.01) s after withdrawal).

Stopping selegiline abolished the posterior circulation symptoms in the one patient with complicated orthostatic hypotension, and considerably diminished or abolished the postural symptoms in all previously affected group II patients (table 4). The mean supine systolic and diastolic blood pressures fell after selegiline withdrawal, but this was not significant. Withdrawal of selegiline caused a severe and disabling decline in motor function in 13 (82%) patients. The daily levodopa dose (mg) was generally increased (table 4), although this was not significant, and seven (44%) patients required pergolide and in one case apomorphine to restore comparable motor function. Within two weeks after selegiline was stopped, seven (44%) patients developed transient orthostatic symptoms. No patient with symptomatic systolic hypotension had bradycardia suggestive of a vasovagal attack. All patients who became dizzy or lost consciousness were symptomatic within three minutes of tilting. No selegiline patient with symptomatic hypotension during tilting was symptomatic on standing, even in the presence of frank hypotension. Severe hypotension on tilting was not related to low supine blood pressure. Diastolic blood pressure was variably affected by tilting and standing (tables 1, 2) and was substantially reduced only in the presence of symptomatic systolic hypotension. Hypotension on tilting was associated with a variable and insignificant increase in heart rate and the normal rise in plasma noradrenaline, which was detected in group I, was absent (table 1). After withdrawal of selegiline, head up tilt did not result in hypotension in any patient, including those who were previously hypotensive and symptomatic, and the normal rise in plasma noradrenaline was restored (table 1, figure).
Selegiline therapy was associated with mild asymptomatic systolic hypotension on standing which resolved after withdrawal of the drug. Comparison between group I and group II: P<0.05, two tailed test. However, drug withdrawal did not cause any autonomic function (comparison between groups I and II: P>0.05, paired t test). NA = not available; BP = blood pressure; HR = heart rate. 3

Table 3: Effects of activating manoeuvres on BP and HR (mean (SEM))

<table>
<thead>
<tr>
<th>group</th>
<th>I levodopa only (n=9)</th>
<th>II selegiline and levodopa (n=16)</th>
<th>II selegiline ceased (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva ratio</td>
<td>1.13 (0.03)</td>
<td>1.15 (0.03)</td>
<td>1.07 (0.02)*</td>
</tr>
<tr>
<td>R/R ratio with deep breathing</td>
<td>4.9 (1.5)</td>
<td>4.3 (0.7)</td>
<td>5.2 (1.0)</td>
</tr>
<tr>
<td>Mental arithmetic</td>
<td>5.4 (2.5)</td>
<td>2.2 (5.5)</td>
<td>1.9 (3.0)</td>
</tr>
<tr>
<td>% Change in systolic BP</td>
<td>6.0 (4.9)</td>
<td>3.1 (2.1)</td>
<td>−3.0 (1.8)</td>
</tr>
<tr>
<td>% Change in diastolic BP</td>
<td>7.9 (2.4)</td>
<td>6.8 (1.8)</td>
<td>5.3 (2.5)</td>
</tr>
<tr>
<td>Response to cold face pack</td>
<td>1.8 (3.7)</td>
<td>−2.3 (3.2)</td>
<td>6.7 (3.3)</td>
</tr>
<tr>
<td>% Change in systolic BP</td>
<td>−0.4 (1.9)</td>
<td>−5.3 (6.3)</td>
<td>3.8 (4.0)</td>
</tr>
<tr>
<td>% Change in diastolic BP</td>
<td>−2.0 (1.2)</td>
<td>−0.8 (1.3)</td>
<td>−2.4 (1.4)</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>4.7 (2.1)</td>
<td>−0.5 (3.3)</td>
<td>NA</td>
</tr>
<tr>
<td>% Change in systolic BP</td>
<td>−0.1 (14.0)</td>
<td>−1.2 (27.2)</td>
<td>NA</td>
</tr>
<tr>
<td>% Change in HR</td>
<td>2.9 (2.5)</td>
<td>2.5 (0.9)</td>
<td>−3.0 (1.7)</td>
</tr>
</tbody>
</table>

As absolute and percentage changes were similar, only the percentage changes are shown. No activating procedure affected blood pressure or heart rate in either group (P>0.05, paired t test). Selegiline did not affect any autonomic function (comparison between groups I and II: P>0.05, two tailed t test), but its withdrawal mildly reduced the Valsalva ratio and reversed the heart rate response to the cold pressor test (P<0.05; P<0.01, paired t test). However, drug withdrawal did not cause any of these indices to differ from those treated with levodopa alone (P>0.05, paired t test). NA = not available; BP = blood pressure; HR = heart rate.

Table 4: Effects of ceasing selegiline on clinical state and levodopa therapy (mean (SEM))

<table>
<thead>
<tr>
<th>group</th>
<th>I levodopa only (n=9)</th>
<th>II selegiline and levodopa (n=16)</th>
<th>II selegiline ceased (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural dizziness</td>
<td>5 (55%)</td>
<td>6 (38%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Symptomatic motor decline</td>
<td>NA</td>
<td>NA</td>
<td>13 (82%)</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>2.4 (0.2)</td>
<td>2.6 (0.2)</td>
<td>3.3 (0.4)*</td>
</tr>
<tr>
<td>NWUDS</td>
<td>45.1 (0.6)</td>
<td>43.4 (0.9)</td>
<td>39.3 (1.8)*</td>
</tr>
<tr>
<td>Webster</td>
<td>11.7 (1.6)</td>
<td>14.7 (1.1)</td>
<td>21.2 (1.4)*</td>
</tr>
<tr>
<td>Daily levodopa dose (mg)</td>
<td>1157 (257)</td>
<td>699.4 (91.3)</td>
<td>777.5 (122.1)</td>
</tr>
</tbody>
</table>

Group I and II patients were matched for disease severity at the onset of the study. After withdrawal of selegiline, motor function declined despite increased daily levodopa and the addition of dopamine agonists in 7 (44%). Comparison between groups I and II: P<0.05; P<0.01, two tailed t test. Comparison between group II and group I after withdrawal of selegiline: P<0.05; P<0.01, paired t test. NA = not applicable.

dysphoria and one (8%) euphoria. Cognition was improved in two (16%) patients and hallucinations disappeared in the sole patient with this symptom.

Discussion

Sustained selegiline therapy over several years was associated with severe and selective systolic hypotension on head up tilt in nine of 16 patients. The diastolic blood pressure was affected only in the presence of severe symptomatic systolic hypotension, whereas there was little tachycardia. Withdrawal of selegiline abolished orthostatic hypotension on head up tilt. The mean supine systolic and diastolic blood pressure falls after selegiline withdrawal, but this was not significant. In a subsequent study (in preparation) we have found a similar fall in supine systolic and diastolic blood pressure which was significant and which we have tentatively interpreted as consistent with a supine pressor effect of selegiline, but the significance and cause of this finding remains uncertain. No patient had multiple systm atrophy and global autonomic failure was excluded by clinical and laboratory investigation, including examination of other cardiovascular reflexes. Thus cryptic autonomic failure or drug interactions did not cause orthostatic hypotension. Volume depletion is unlikely to have contributed as all patients were examined in the morning after a normal breakfast and maintained fluid intake before testing. Severe symptomatic selegiline induced hypotension has been reported in multiple system atrophy71 and is a recognised complication of selegiline therapy in Parkinson's disease.7 Selegiline was recently reported to be associated with hypotension on head up tilt in Parkinson's disease.72

The study was open and all eligible patients on levodopa alone or levodopa and selegiline seen in our clinic over four successive months were recruited, regardless of their symptomatology; all completed the study. Thus possible selectivity bias in the study design was minimised. A potential criticism is that nine patients were recruited in group I versus 16 in group II. However, the two groups were well matched for age, disease severity, and disease duration, although the daily dose of levodopa and incidence of postural dizziness in group I was greater. Postural hypotension resolved after withdrawal of selegiline even though the daily dose of levodopa was generally increased and potentially hypertensive agonists were prescribed in seven patients (44%). Thus it is unlikely that the difference in numbers reflects a selection bias towards more pronounced underlying autonomic dysfunction in patients placed on selegiline. At the time of the study, which was immediately after publication of the UKPDRG trial,4 most patients had been placed routinely on selegiline and levodopa for some years as a result of the initial DATATOP findings.3 We think that this accounts for the difference in the size of the groups.

The mechanism of the hypertensive effect of selegiline is unclear. Few patients took drugs other than levodopa, excluding a drug interaction other than with levodopa. We have subsequently found a similar hypotensive effect in a patient on selegiline monotherapy. None the less, it is not possible to determine if the hypotension found by us was due to selegiline alone or to an interaction with levodopa. Maintenance of systolic blood pressure during passive tilt is thought to be dependent on cardiac output and total peripheral vascular resistance.23 Cardiac output is dependent on heart rate, venous return, and cardiac contractility.41 Heart rate rose equally in group I and group II patients before stopping selegiline and was unaffected by head up tilt in group II patients after drug withdrawal. These results imply that cardiac contractility was impaired in those on levodopa and selegiline, assuming that total cardiac contractility was impaired in those on levodopa and selegiline.
Peripheral resistance and venous return, which were not measured, did not fall precipitously. Plasma noradrenaline was increased in response to head up tilt in group I and in group II after withdrawal of selegiline, but fell in those receiving selegiline. The rise in plasma noradrenaline in those not receiving selegiline was not significant, even though typical of the normal response for our laboratory. However, as suggested by the large SEM, there were considerable differences in concentrations between patients which may have masked a real physiological effect of head up tilt on plasma noradrenaline with such small numbers. Standing for two minutes caused a small but symptomatic fall in systolic and diastolic blood pressure accompanied by a rise in heart rate in group II patients which was abolished by stopping selegiline and which was not seen in group I (table 2). Presumably, the fall in systolic blood pressure was due to the same effects on cardiac output as occurred with tilting. Diastolic blood pressure after standing for two minutes is maintained by increased sympathetic activity as evidenced by the rise in heart rate. Overall, these results suggest that selegiline in combination with levodopa was associated with impaired cardiac output, whereas sympathetic function was probably also impaired as failure of heart rate and plasma noradrenaline to increase with hypotension is thought to indicate autonomic failure.

The techniques used in this study do not discriminate between the peripheral effenter, peripheral afferent or central components of the autonomic nervous system. Dysfunction of each part of the autonomic system, all of which are affected in Parkinson’s disease, may cause orthostatic hypotension. Thus, the level(s) of the autonomic system involved in systolic hypotension induced by selegiline in combination with levodopa are uncertain. Similarly, the mechanism(s) by which selegiline might induce orthostatic hypotension is unknown. Non-selective MAO inhibitors which inactivate both isoenzymes and which are not metabolised to amphetamines, cause orthostatic hypotension, possibly because of inhibition of tyramine metabolism. Short term studies of selegiline at doses of 10 mg/day found that the drug only mildly enhanced the pressor effects of tyramine, consistent with partial blockade of MAOA and pronounced inhibition of MAOB. Long term exposure to selegiline has been associated with progressively increasing inhibition of MAOA in rats and humans raising the possibility that a similar effect due to increased plasma tyramine could have resulted from chronic therapy at 10 mg/day. Selegiline is metabolised to metamphetamine and amphetamine. The psychiatric symptoms in 52% of patients after drug withdrawal and previous evidence in humans and rats suggest that selegiline exerts an amphetamine like effect in vivo. The selective hypotensive effects of selegiline on systolic blood pressure found in this study were similar to those of amphetamine and metamphetamine in human volunteers. Chronic exposure to amphetamine also results in tachyphylaxis of the pressor effects of the drug, reduces cardiac output in dogs, reduces striatal dopamine and tyrosine hydroxylase in humans and is neurotoxic to nigrostriatal dopaminergic terminals in experimental animals. Selegiline has been reported to be neurotoxic to cultured dopaminergic neurons. It is not known if these drugs are similarly toxic to sympathetic neurons in humans.

In the UKPDRG study, the mortality of those on selegiline in combination with levodopa began to increase after three years, whereas detailed studies of the toxicology of selegiline have been for shorter periods. The cause of the increased mortality in the UKPDRG study has not been identified, but further information will be available after completion of the cause of death examination (CODE) study. One patient in the present study with recurrent orthostatic hypotensive strokes was clearly at risk of selegiline induced mortality and another with ventricular tachycardia may have been so. If patients with orthostatic hypotension on tilting are included, 56% of the patients in this series had morbidity attributable to selegiline. Clinical studies of selegiline have shown a low incidence of symptomatic orthostatic hypotension, but did not assess changes with head up tilt and plasma concentrations of amphetamine and metamphetamine were estimated only indirectly via urinary concentrations which were comparable with those seen after oral amphetamine ingestion. Our finding that standing blood pressure and prior orthostatic symptoms are poor indicators of hypotension induced by head up tilt suggests that the hypotensive actions of selegiline may have previously been underestimated. As amphetamines cause cardiac arrhythmias, intracranial haemorrhage and occlusive cerebral vasculitis in normal humans, an amphetamine effect may indicate an increased risk of cardiovascular or cerebrovascular toxicity. Experience of amphetamines in Parkinsonism is extremely limited, but benzodrine sulphate therapy over weeks variably affected supine blood pressure (“increased, decreased, unchanged, or vacillating”) in postencephalitic Parkinsonism and a two week course of amphetamine modestly affected supine blood pressure, but was not reported to cause postural dizziness, in Parkinson’s disease.

The relation between our finding that selegiline in combination with levodopa has cardiovascular toxicity and the increased mortality associated with this drug regimen in the DATATOP trial is uncertain. In DATATOP, which did not examine mortality as a primary endpoint or report selegiline induced mortality, patients received levodopa only when their symptoms were uncontrolled by the trial drugs. The projected median time at which DATATOP patients randomised to selegiline alone required levodopa was 2.02 years, which is substantially less than the duration of selegiline therapy in our patients (mean 6.4 years). Thus the patients in our study were not typical of those in the DATATOP trial.
Whether or not the rare patient with Parkinson's disease on selegiline monotherapy after three years is at risk of orthostatic hypotension is unknown. Withdrawal of selegiline resulted in a severe symptomatic motor decline in 82% of patients necessitating increased dopaminimetics and confirming a pronounced levodopa sparing effect.7 8 9 Thus the UKPDRG10 and DATATOP11 studies and our results are consistent with selegiline acting in Parkinson's disease only by alleviating motor symptoms.

Conclusion

We have shown that the risks of selegiline in combination with levodopa causing orthostatic hypotension in Parkinson's disease have been underestimated. Whether or not selegiline alone has similar cardiovascular toxicity is uncertain. It seems prudent to withdraw selegiline from those with symptomatic postural hypotension or concomitant cardiovascular or cerebrovascular disease. For those already on selegiline without appreciable symptomatic morbidity, but with a greater than 20 mm Hg fall in blood pressure on standing for two minutes, gradual withdrawal with a concomitant titration of levodopa requirements should be considered.

We thank Mrs Katherine Blasealled-Barr (Autonomic Unit, National Hospital for Neurology and Neurosurgery) for invaluable assistance with the autonomic studies and Laura Watson (Autonomic Unit, Institute of Neurology and Neurovascular Medicine Unit, Imperial College of Medicine at St Mary's Hospital, London) for measuring the plasma catecholamine concentrations. AC is the beneficiary of a Kate Stillman Fellowship.


Cognitive recovery instead of decline after acute encephalitis: a prospective follow up study
Laura Hokkanen and Jyrki Launes

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