Neuronal number and volume alterations in the neocortex of HIV infected individuals

Ian Paul Everall, Philip J Luthert, Peter L Lantos

Abstract

Substantial neuronal loss in the superior frontal gyrus in patients who have died of AIDS have been reported previously. This investigation examined the distribution of neuronal loss in three other neocortical areas and, alteration in neuronal volume in four neocortical areas. This was carried out using two stereological probes, the “disector” and the “nucleator”. These recently developed methods provide estimations, regardless of size and shape, in real three-dimensional space, and are more efficient than conventional quantitation. The study was performed on 12 HIV infected individuals and nine controls. The HIV group had no neuropathological evidence of opportunistic infections or neoplasms, five had HIV encephalitis and the remaining seven had only minimal pathology. There was significant neuronal loss of 30% (p = 0.018) in the calcarine cortex (primary visual area), and loss of 18% in the superior parietal lobule which just failed to reach significance. This loss was not related to the presence of HIV encephalitis. The mean neuronal volume was increased in the occipital area by 29% (p = 0.028) and the frequency of large neurons (over 2000 µm²) doubled in the frontal (p < 0.05) and parietal (p < 0.02) areas. The results confirm the hypothesis that HIV infection is associated with neuronal injury and death, and suggest that increase in neuronal size may be a feature of the cytopathology of this condition.

(J Neurol Neurosurg Psychiatry 1993;56:481–486)

Neuropathological studies have revealed that human immune deficiency virus (HIV) induces a variety of brain lesions, including HIV encephalitis, HIV leukoencephalopathy, lymphocytic meningitis and diffuse poliodystrophy.1 Although clinico-neuropathological correlations are tenuous, Navia et al,4 suggested that the degree of dementia, occurring in patients with AIDS, was related to the severity of HIV encephalitis, characterised by multinucleated giant cells. Two years later Price et al,6 re-analysing results pooled from other smaller studies, observed that patients with marked dementia had multinucleated giant cells in the brain at post mortem, while those with mild or no dementia had fewer such cells. This conclusion is still preliminary as the observations were made of different sets of patients, with differing (25–50%) rates of post mortem examination. Thus HIV encephalitis, as a pathological substrate for the dementia, has yet to be confirmed.

Recent quantitative studies have, however, revealed that HIV infection of the brain also results in substantial neuronal loss,5,7 but the extent and distribution of this loss is still under investigation. N-acetyl aspartate (NAA) is an amino acid, occurring mainly in neurons,4 that can be demonstrated by magnetic resonance spectroscopy (MRS). The reduction in the amount of NAA in patients with AIDS, as estimated by MRS, may indicate neuronal loss.7 Neuronal loss is an obvious pathological substrate for the clinical disorder HIV dementia, and knowledge of the mechanism and effect of HIV on neuronal populations is essential, not only for the understanding of the pathogenesis of HIV induced neurological syndromes, but also for devising scientifically based treatments for these conditions. This report complements the previous study on neuronal loss in the frontal cortex4 by assessing the neuronal numerical density (number per unit volume) in the three other neocortical areas and by estimating neuronal volume measurements in all four cortical areas.

Methods

The methods and clinical cases have been described previously4. Briefly, 12 consecutive cases, without HIV-associated opportunistic infection or neoplasm, were selected from the Medical Research Council Central AIDS Brain Tissue Bank. Five of these brains had the sole neuropathological diagnosis of HIV encephalitis, the hallmark being the presence of multinucleated giant cells2 and other characteristics including the presence of macrophages and microglia. The remaining seven had only minimal changes including slight astrocytosis and perivascular cuffing by inflammatory cells. In this report there was one additional HIV case not available to the earlier study. The HIV group was compared with eight control cases, which have been described earlier.4 All cases were male, and the mean (SD) age in each group was 36:2 (8:2) for the HIV group and 45:3 (12:8) years for the control group. Student’s t test revealed no significant difference in age between the two groups.

The following areas were examined: the
superior frontal gyrus at the level of the genu of the corpus callosum, the inferior temporal gyrus at the level of the lateral geniculate body, superior parietal lobule at the level of the splenium of the corpus callosum, and the calcarine cortex of the occipital lobe. The tissue was embedded in paraffin wax on a five day processing cycle. Tissue shrinkage, throughout the process, was measured and found to be the same in each group. Sections were cut at 20 μm, stained with cresyl-violet and coded for assessment blind to the diagnosis.

Two stereological probes were used: the “disector” and the “nucleator”, for estimation of the neuronal numerical density and volume respectively. Essentially the optical “disector” is a stereological probe designed to be specifically sensitive to estimating the number of objects, such as neurons, present in a specimen. This technique is advantageous over traditional methods of quantification in that it is unbiased, that is, neurons are sampled and counted regardless of their shape or size. The “disector” is a three-dimensional probe composed of two counting frames or grids, of known area, vertically parallel to each other within the section, and separated by a known distance (5 μm). In practice, this is achieved by projecting the counting frame onto the section, focusing down through the required distance where the parallel projected frame is situated. This results in the probe counting those neurons that occur within the test volume, which is composed of the area of the frame multiplied by the distance between the two frames. The “nucleator” is an evolution of the “disector” and is used in conjunction with it. It facilitates the estimation of the volume of every sampled neuron by placing a ruler, in a random orientation, through the nucleolus of the neuron and measuring the distance from side to side. The ruler is designed to be graduated in cubed distances. In this investigation it was constructed to comprise 10 size classes, which were the cube roots of the integers one to 10. The measurement of cubed size therefore confers an estimate of neuronal volume. The theoretical principles of these two probes together with the formulae and their derivations are found elsewhere.

The estimation was performed, on a Zeiss H16 microscope with a Heidenhain VRZ403 electronic length gauge measuring vertical movement. The measuring volume was applied continguously across the cortical ribbon, once at each location, from the grey-white matter junction to the pial surface, at a magnification of ×1400 with a ×100 objective, logarithmically to 5, under oil immersion, providing a depth of field of 0.24 μm, as calculated by Williams and Rakic. Neurons were only counted if they fell within the three dimensional measuring volume of the “disector” and as long as they were not overlapping two forbidden lines on the grid (the left and lower sides). Neurons were identified by a clear nuclear profile containing a nucleolus and Nissl substance in the cell body.

The statistical analysis was performed by either a Student’s t test or analysis of variance, and where appropriate the data were transformed to stabilise unequal variances. A significant analysis of variance was followed by comparison of means, for the two HIV subgroups and the control group, by the Fcomp ratio to identify the direction of the difference. This calculates the level of significance for observed differences in between group comparisons.

**Results**

1) **NEURONAL NUMERICAL DENSITY**

The neuronal numerical density was estimated for the temporal, parietal and occipital neocortical areas. The analysis was undertaken in two stages: firstly, by comparing the HIV and control groups, using a Student’s t test, and then secondly, by subdividing the HIV group into those with HIV encephalitis (five cases) and those with only minimal changes (seven cases) and comparing these with the control group by analysis of variance. The estimations for the frontal area, described elsewhere, revealed a significant loss of 38% in both the HIV encephalitis and minimal change subgroups compared to the control group.

1-1) **ANALYSIS OF TWO GROUPS**

Table 1 displays the neuronal numerical density (number of neurons \( \times 10^3 \text{ mm}^{-3} \)) for each case in the HIV infected and control groups together with the group mean and standard deviation in the temporal, parietal, and occipital neocortical areas. The variances were stable for the two groups in each area (F (12, 8) <2, not significant). In the occipital area there was a reduction in neuronal number from 703 in the control group to 490 \( (\times 10^3 \text{ mm}^{-3}) \) in the HIV group, representing a significant loss of 30% (p = 0.018). In the parietal area there was a reduction in the number of neurons from 566 to 464 \( (\times 10^3 \text{ mm}^{-3}) \), a loss of 18%, however, statistical analysis revealed this to be just below the level of significance (p = 0.079). In the temporal area there was no significant difference between the two groups in the neuronal numerical density (p = 0.85).

<table>
<thead>
<tr>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>CONT</td>
<td>HIV</td>
</tr>
<tr>
<td>H1 378</td>
<td>C1 329</td>
<td>C1 562</td>
</tr>
<tr>
<td>H2 351</td>
<td>C2 331</td>
<td>C2 379</td>
</tr>
<tr>
<td>H3 282</td>
<td>C3 436</td>
<td>C3 400</td>
</tr>
<tr>
<td>H4 290</td>
<td>C4 519</td>
<td>C4 595</td>
</tr>
<tr>
<td>H5 474</td>
<td>C5 570</td>
<td>C5 700</td>
</tr>
<tr>
<td>H6 385</td>
<td>C6 311</td>
<td>C6 632</td>
</tr>
<tr>
<td>H7 474</td>
<td>C7 433</td>
<td>C7 552</td>
</tr>
<tr>
<td>H8 413</td>
<td>C8 541</td>
<td>C8 506</td>
</tr>
<tr>
<td>H9 462</td>
<td>H9 523</td>
<td>H9 342</td>
</tr>
<tr>
<td>H10 279</td>
<td>H10 316</td>
<td>H10 421</td>
</tr>
<tr>
<td>H11 517</td>
<td>H11 348</td>
<td>H11 214</td>
</tr>
<tr>
<td>H12 381</td>
<td>H12 443</td>
<td>H12 692</td>
</tr>
<tr>
<td>Mean 591</td>
<td>384</td>
<td>464</td>
</tr>
<tr>
<td>SD 81</td>
<td>73</td>
<td>135</td>
</tr>
</tbody>
</table>

Cases H1–H12 are HIV, and C1–C8 are controls. CONT = control. SD = standard deviation.
Neuronal number and volume alterations in the neocortex of HIV infected individuals

Table 2 The neuronal numerical density in the superior parietal lobule in the two HIV subgroups, encephalitis and minimal change, and the control group (\( \times 10^7 \text{ mm}^{-3} \)), together with the group means and standard deviation.

<table>
<thead>
<tr>
<th>Case</th>
<th>HIV Encephalitis</th>
<th>Case</th>
<th>HIV Minimal change</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>600 H2 640 H4 735 H5 377 H11 441</td>
<td>H3 427 H7 523 H8 316 H9 348 H10 443 H12 382</td>
<td>C1 562 C2 379 C3 600 C4 595 C5 700 C6 632 C7 552 C8 506</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>559</td>
<td>SD 147</td>
<td>396</td>
<td>73</td>
<td>566</td>
</tr>
</tbody>
</table>

SD = standard deviation.

Table 3 The neuronal numerical density in the calcicarne cortex of the occipital lobe in the two HIV subgroups, encephalitis and minimal change, and control groups (\( \times 10^7 \text{ mm}^{-3} \)), together with the group means and standard deviation.

<table>
<thead>
<tr>
<th>Case</th>
<th>HIV Encephalitis</th>
<th>Case</th>
<th>HIV Minimal change</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>862 H2 492 H4 733 H5 294 H11 561</td>
<td>H3 342 H7 514 H8 692 H9 336 H10 328 H12 421</td>
<td>C1 485 C2 525 C3 622 C4 729 C5 908 C6 871 C7 846 C8 636</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>588</td>
<td>SD 219</td>
<td>410</td>
<td>140</td>
<td>703</td>
</tr>
</tbody>
</table>

SD = standard deviation.

1-2) ANALYSIS OF TWO HIV SUBGROUPS AND THE CONTROL GROUP

Before the estimations it was known that the HIV infected group was divided into two subgroups: five cases with HIV encephalitis and seven cases with minimal neuropathological abnormalities. To examine whether neuronal loss was associated with the presence of HIV encephalitis the two subgroups were tested against the control group using analysis of variance. In two of the brain areas, as shown in tables 2 and 3, there were significant group differences: parietal (F(2, 17) = 5.94, p < 0.05) and occipital (F(2, 17) = 5.2, p < 0.05). In the temporal area, however, there was no significant difference between the two HIV subgroups and the control group (F(2, 17) = 0.64).

For the two areas, parietal and occipital, demonstrating differences in neuronal numerical density a comparison of the means by the F\(_{\text{comp}}\) ratio was calculated. In the parietal area the HIV minimal change group was significantly different from the HIV encephalitis group (F\(_{\text{comp}}\) (1, 17) = 7.21, p < 0.05) and the control group (F\(_{\text{comp}}\) (1, 17) = 10.05, p < 0.05). However, the HIV encephalitis group did not differ from the control group (F\(_{\text{comp}}\) (1, 17) = 0.01, not significant). In the occipital area the only significant difference was between the HIV minimal change and control group (F\(_{\text{comp}}\) (1, 17) = 10.35, p < 0.01). Thus in both areas the most significant contribution to the decrease in neuronal numerical density in the HIV group for these two areas was identified as those cases with only minimal neuropathological changes.

2) NEURONAL VOLUME CHANGES

The estimation of neuronal volume was performed in four neocortical areas: frontal, parietal, temporal and occipital.

2-1) MEAN NEURONAL VOLUME CHANGES

The neuronal volume for each case in the four areas plus the mean neuronal volume and standard deviation for each group is shown in table 4. No significant difference was found in the mean neuronal volume (\( \mu\text{m}^3 \)) between the HIV and control groups for both the parietal area (p = 0.49) or the temporal area (p = 0.95). In the frontal lobe there was an approximately 18% increase in neuronal volume in the HIV group, which was just below the level of significance (p = 0.074). The occipital area demonstrated a 29% increase in neuronal volume. Following logarithmic transformation of the data, to stabilise the variances, this increase, in the occipital area, was found to be highly significant (p = 0.028). In neither area was there any significant difference in volume changes in either of the two HIV subgroups.

2-2) NEURONAL VOLUME CHANGES IN DIFFERENT SIZE GROUPS

To examine further the alterations in neuronal volume the neurons were arbitrarily divided into three groups: small (less than 1000 \( \mu\text{m}^3 \)), medium (1000–2000 \( \mu\text{m}^3 \)), and large (greater than 2000 \( \mu\text{m}^3 \)). Table 5 shows the mean frequency of small, medium and large neurons for each area in the two differ-

Table 4 The mean neuronal volume (\( \mu\text{m}^3 \)) for each case in each area and the mean (SD) for each group.

<table>
<thead>
<tr>
<th>Frontal</th>
<th>Occipital</th>
<th>Parietal</th>
<th>Temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>CONT</td>
<td>HIV</td>
<td>CONT</td>
</tr>
<tr>
<td>H1 1161</td>
<td>C1 692</td>
<td>H1 782</td>
<td>C1 845</td>
</tr>
<tr>
<td>H2 1108</td>
<td>C2 780</td>
<td>H2 1158</td>
<td>C2 740</td>
</tr>
<tr>
<td>H3 1169</td>
<td>C3 961</td>
<td>H3 1315</td>
<td>C3 751</td>
</tr>
<tr>
<td>H4 1077</td>
<td>C4 1360</td>
<td>H4 812</td>
<td>C4 937</td>
</tr>
<tr>
<td>H5 1057</td>
<td>C5 937</td>
<td>H5 962</td>
<td>C5 1019</td>
</tr>
<tr>
<td>H6 929</td>
<td>C6 1059</td>
<td>H6 857</td>
<td>C6 594</td>
</tr>
<tr>
<td>H7 1482</td>
<td>C7 881</td>
<td>H7 1412</td>
<td>C7 756</td>
</tr>
<tr>
<td>H8 889</td>
<td>C8 980</td>
<td>H8 838</td>
<td>C8 679</td>
</tr>
<tr>
<td>H9 995</td>
<td>H9 769</td>
<td>H9 709</td>
<td>H9 989</td>
</tr>
<tr>
<td>H10 992</td>
<td>H10 1517</td>
<td>H10 963</td>
<td>H10 1119</td>
</tr>
<tr>
<td>H11 1528</td>
<td>H11 870</td>
<td>H11 1264</td>
<td></td>
</tr>
<tr>
<td>H12 1050</td>
<td>H12 917</td>
<td>H12 1377</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1128</td>
<td>957</td>
<td>1017</td>
</tr>
<tr>
<td>SD</td>
<td>195</td>
<td>202</td>
<td>264</td>
</tr>
</tbody>
</table>

CONT = control, SD = standard deviation.
ent groups. In the temporal area there was no difference in the size distribution of small, medium or large neurons in the HIV and control groups.

In contrast, the frontal, parietal and occipital areas all demonstrated differences in the distribution of neuronal sizes between the HIV and control groups. In these three areas there was a reduced frequency of small neurons in the HIV group, but this was only significant in the occipital area, a reduction of 15% (p < 0.05, on the log transformed data). In the large neuronal class the situation was reversed with all three areas having more than double the frequency observed in the control group. This was statistically significant in the frontal area (p < 0.05) and the parietal area (p < 0.02, on the log transformed data). In the occipital area, however, this difference did not achieve statistical significance. This may have been due to the fact that in this area large neurons were rarely seen and six of the cases failed to register any neurons in the large class. This will have reduced the power of the test and hence may have contributed to the lack of significance.

Discussion

This study complements our previous work on the frontal cortex. Together, they characterise the neuronal numerical density and neuronal volume in four neocortical areas. In HIV infection of the brain, there is evidence for cerebral atrophy from neuroimaging studies and possibly for neuronal loss from magnetic resonance spectroscopy. Thus a reduction in neuronal numerical density, as shown in this study, will also obviously represent neuronal loss. Alterations in numerical density can, theoretically, be the consequence of tissue shrinkage which can be excluded by calculating the entire neuronal number per neocortical area or the entire neocortex. Nevertheless, this manner of sampling is problematic in that it can potentially fail to detect focal neuronal loss. Furthermore, if counts within a defined cortical area are made, there is an assumption that each region can be repeatedly and readily identified in a consistent manner acceptable to various research groups.

In this study the neuronal numerical density was found to be reduced by 18% in the superior parietal area and 30% in the calcarine cortex of the occipital lobe. In the latter area there was a highly significant reduction, while in the parietal area it was just below the 0.05 level of significance. It is known that the frontal area neuronal numerical density is reduced by 38% in the HIV group. On analysing differences between the two HIV subgroups and the control group, there was a highly significant neuronal loss (p < 0.01) in the HIV minimal change group in both the occipital and parietal areas. In neither area did neuronal loss appear to be dependent on the presence of HIV encephalitis, as in these two areas, there was no significant difference in the neuronal numerical density between the control and HIV encephalitis groups. By comparison, the frontal area revealed 38% neuronal loss which was equal in both the HIV subgroups.

The reduced neuronal numerical density, in the HIV group, is consistent with significant neuronal loss. This does not appear to be related to the presence of HIV encephalitis but to the superimposition of temporal lobe or occipital or calcarine cortex of the occipital lobe. There was no evidence of loss in the inferior temporal cortex. An analogous study demonstrated loss of 30–50% of large neurons (200–500 μm²), in a sample of eight cases with HIV encephalitis and 10 controls, in the mid-frontal, inferior parietal and superior temporal areas. Our results differ in two ways: in the discrepancy of findings in the temporal area, and in the relationship of neuronal loss to HIV encephalitis. The contrasting results in the temporal cortex may reflect true dissimilarities between the inferior and superior temporal areas. The different results concerning neuronal loss in HIV encephalitis may reflect true differences between the British and American samples or a difference in the methods of assessments. The eight cases examined by Wiley et al had severe white matter and deep grey gliosis with microglial nodules and multinucleated giant cells, while the degree of HIV encephalitis in the five cases in our study may be less severe. Moreover, there were technical differences between the two studies, in that Wiley et al performed quantitation by a computer-assisted image analysis in a two dimensional grid. The accuracy of such measurements is diminished by being biased to counting larger sized neurons and require compensation for optical distortions due to section thickness. Furthermore, computer-assisted image analysis methods, recording cells purely by size and not other cytological features, can be problematic in attempting to identify specific cell populations in the brain, glial cells can be mistaken for small neurons and, there is a tendency to over estimate the presence of large neurons.

This study involved the application of a three-dimensional stereological probe, the “nucleator.” This probe uses the “disector” as a sampling frame in which a ruler with cubed gradations is applied, in a random orientation through the nucleolus, to provide an estimate of neuronal volume. The results
show that, apart from the inferior temporal area, there is a shift in the neuronal volume in the HIV group from smaller to larger neurons. The decline in the frequency of small volume neurons is significant in the occipital area, while remaining a trend in the frontal and parietal area. The doubling in the frequency of large volume neurons is significant in the frontal and parietal areas, while only a trend in the occipital area. The differing significance in the alteration of small and large neurons in the various neocortical areas is complicated by two factors. Firstly, the range of neuronal size is so large that there is considerable variability in sampling between cases, thus increasing, and often making unequal, the sample variances. Secondly, in the occipital area, with its more uniformly smaller neurons, the variability between cases was less and so changes in small volume neurons was easily detected statistically while the relative paucity of large volume neurons reduced the ability of the statistical analysis to identify differences.

Overall, the results from this study demonstrate that HIV infection of the brain is associated with significant neuronal loss in various neocortical areas. Neuronal loss is a recognised feature of ageing in the superior and mid-frontal gyrus and occipital area. Similar studies have also found disparity in the degree of neuronal loss between the superior and inferior temporal areas. Both a comprehensive early investigation into the organisation of the cerebral cortex and a study by Henderson et al. revealed that the inferior temporal gyrus showed the least change in cell number. This may indicate a resistance to degenerative disease. In Alzheimer’s disease the neuronal loss is reported to be more severe, for example, 40% in the frontal region and 46% in the superior temporal area. This was 20% more than in the age-matched brain, and this severe loss may be important in the production of clinical features. In patients with AIDS while neuronal loss can occur in the presence of HIV encephalitis, it is not necessarily the result of that inflammatory lesion and may in fact be due to an independent mechanism. Most importantly, the results of this investigation support the notion that a component of the cytopathology is a swelling of the neuron in response to injury. This is indicated by the reduction in the frequency of small neurons and an increase in large neurons in the HIV group.

Two questions remain: primarily, what is the mechanism of this injury, and secondly, why does it occur in certain neocortical areas. As there is no evidence for direct infection of neurons by HIV, a number of mechanisms have been outlined. Firstly, HIV infected inflammatory cells are thought to produce cytokines which may cause neuronal damage. If cytokines are involved in neurotoxicity then our results indicate that the multinucleated giant cells, pathognomonic of encephalitis, may not be important sources of cytokines and that other inflammatory cells such as macrophages or microglia, which are increased in number in the cortex, may be more important. Other observations support the potential role of neurotransmitters, especially vasoactive intestinal peptide (VIP) and glutamate. VIP, which is present throughout the cortex, has sequence homology with gp120, a HIV envelope glycoprotein. VIP has been shown to prevent gp120 induced neuronal death in cell culture. In addition, glutamate antagonists can also prevent gp120 induced neuronal death. Both neurotransmitters regulate calcium entry and it is thought that gp120 causes an early rise in intracellular calcium and subsequent cell death. Glutamate, or a glutamate agonist, may be synergistic in this toxicity. An important feature is that, while both VIP and glutamate are extensively distributed throughout the neocortex, the frontal and occipital areas may have higher levels, and the frontal area appears to be especially rich in glutaminergic neurons. There is in vivo evidence for the interaction of excitotoxins and gp120, as a mechanism for neuronal loss leading to cognitive impairments, from a study demonstrating that the level of quinolinic acid, an endogenous glutamate agonist, in the CSF, is directly related to the degree of neuropsychological deficits. Further evidence implicating calcium induced neuronal death is the similarity in structure and function of HIV env and nef products to venous toxins which interact with monovalent cation channels. Such toxins can induce transmembrane ion fluxes and cell swelling resembling the “ballooning” degeneration induced by HIV isolates.

The putative role of neurotransmitters and calcium in neuronal death would also rationalise the different effect on the various neocortical areas which may be due to differing populations of VIPergic and glutaminergic neurons. As significant neuronal damage and loss has now been demonstrated, it is important to correlate these neuropathological findings to clinical cognitive abnormalities so that the pathological substrate of the dementia can be understood and treated.

We thank the Medical Research Council National AIDS Neuropathology Database and Brain Tissue Bank and Miss J Davies, Coordinator, for providing the material. Mrs H Barnes for technical preparation of the material; Dr G Dunn, Department of Biostatistics and Computing, for statistical advice; the Medical Research Council for support of IPE; the Mason Medical Foundation; and the clinicians and pathologists who helped in this study.


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*J Neurol Neurosurg Psychiatry* 1993 56: 481-486
doi: 10.1136/jnnp.56.5.481

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