Gliial cytoplasmic inclusions are not exclusive to multiple system atrophy

In 1989 Papp et al. reported finding argyrophilic inclusions in the cytoplasm of oligodendrocytes in cases of multiple system atrophy, and their presence in the sporadic form of this condition has since been confirmed. The importance of gliarial cytoplasmic inclusions as a diagnostic hallmark of multiple system atrophy has been emphasised by one of the authors as well as by others. At the UK Parkinson's Disease Society Brain Bank in London, tissue is donated by patients with principally movement disorders. Gliarial cytoplasmic inclusions occurred in all brains from patients with multiple system atrophy (total 56); however, in three of seven cases with a pathological diagnosis of corticobasal degeneration and two of 18 cases with Steele-Richardson-Olszewski syndrome similar intracytoplasmic oligodendrocyte inclusions were identified. These were filamentous argyrophilic structures (figure) immunoreactive with tau and ubiquitin antibodies. In corticobasal degeneration they were most numerous in white matter underlying the affected cortex, in the corpus callosum, internal capsule, and in one case, the basis pedunculi; occasional similar inclusions were also identified in the affected cortical and in the brain stem as well as in cerebellar hemispheric white matter, in the absence of any neuronal abnormalities. In the cases of Steele-Richardson-Olszewski syndrome inclusions were most prominent in cerebellar white matter. We have not counted or mapped the distribution of gliarial inclusions in our cases, but have the impression that they are less numerous than in multiple system atrophy.

These findings have important implications for histological diagnosis and our understanding of disease pathogenesis. There is increasing awareness of overlap between many neurodegenerative conditions, in particular those associated with parkinsonism; thus the Lewy body, Pick body, neurofibrillary tangle, or the gliarial cytoplasmic inclusion are not exclusive to any of the conditions in which they abound. One explanation may be that neurons and glia have a limited repertoire of responses to a variety of different stimuli, resulting in morphological similarities between very distinct neurodegenerative diseases. Alternatively, shared pathogenetic pathways may underlie the cytoskeletal abnormalities seen in these conditions, the exact pattern of pathology being dictated by host factors such as age of exposure and genotype.

Is visual neglect body-centric?

One theory of unilateral visual neglect proposes that it results from disruption of representations of space. But what exactly is the nature of the spatial map that is disrupted? Is it retinotopic, head-centric, body-centric, mapped with respect to gravity, or even possibly object centred? Many of those who have been attracted by representational hypotheses have suggested that it may be body-centric. In other words, the hemispace that patients with left sided visual neglect fail to attend to is that to the left of the body sagittal midline.

Evidence in favour of a disruption of body-centric (or socalled egocentric) spatial representation has been presented from measurements of saccadic latency to briefly illuminated targets with the head turned at various angles with respect to the trunk. Furthermore, Heilman and Valenstein have shown that line bisection is more accurate when the task is presented to the right of the body midline. Cancellation tasks are another way of assessing neglect. If left sided visual neglect is body-centric there should be amelioration, or even complete absence, of neglect when the task is performed in the hemispace right of the body midline.

Eight right handed patients presenting acutely with visual 45° right turned trunk were examined. All of them had left sided visual neglect on the day of presentation; some also had left sided hemiplegia or somatosensory loss. Nine of the patients were considered to have a substantial visual field loss on clinical examination at the bedside. (Assessment of the left half of the visual field was aided by cueing attention, but not gaze, to the left. Patients were asked to fix their gaze on the author and simultaneously encouraged to say whether relatively large objects—for example, flowers—on the left were being moved. Once patients were accustomed to fixing their gaze on the author the experimenter knew when they thought that they had completed the task. After a short break, the task was presented on the other side, the body midline. Patients performed the second trial with the head turned 45° to the right and the trunk held still in the original position. The table showed the results of the experiment. As expected, patients cancelled more of the right half of the cancellation sheet (by contrast with patients with only visual field loss, who are able to cancel targets on both sides of the paper).

The mean cancellation score when head and trunk were aligned was 6-7 (SD 4-7) items; when the head was turned to the right it was 5-9 items (SD = 5-2). There was no significant difference in performance between these two conditions (paired t = 1-1, df = 14, p = 0-3). Thus patients performed just
Patient characteristics and cancellation scores

<table>
<thead>
<tr>
<th>Patient (age)</th>
<th>Lesion</th>
<th>Days after stroke</th>
<th>Items cancelled in front*</th>
<th>Items cancelled in right space†</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (70)</td>
<td>R parietal</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>B (66)</td>
<td>R parietal</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>C (86)</td>
<td>R parietofrontal</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D (65)</td>
<td>R parietal</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>E (80)</td>
<td>R frontal</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>F (67)</td>
<td>R frontal</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>G (71)</td>
<td>R frontal</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>H (77)</td>
<td>R frontal</td>
<td>1</td>
<td>14</td>
<td>17</td>
</tr>
</tbody>
</table>

*When head midline is aligned with body midline. †When head midline is turned 45 degrees to the right of body midline.

as badly when the cancellation task had to be performed in the hemisphere right of the body midline. Unilateral visual neglect therefore does not seem to be body-centric.

This conclusion contradicts that of the two previous reports. There are at least three possible explanations. Firstly, the method employed here—a cancellation task—has never previously been used to assess the co-ordinate frame of neglect. Secondly, there is a possibility that because the sample size is small (n = 8), the conclusion is not representative of all patients with neglect. The same may be said, however, of the other studies cited. A third possible explanation is that the tasks used in the previous studies assessed different brain functions examined by cancellation tasks. It is not possible to say which, if any, of these explanations is correct.

Although the results of this study suggest that neglect is not body-centric, they do not exclude the general proposition that it is a deficit in representing space. It remains a possibility that the disrupted representation is mapped in another coordinate frame.

Two studies have examined the pattern of visual inattention. When patients are either reclined or tilt their heads to the left or right. Both found that irrespective of head position, inattention was worse to the left of the environmental vertical. But both investigations also showed that neglect moved with the head: patients attended less to the left of the head midline, whatever its orientation, as well as attending less to the left of the environmental vertical.

Another study investigated how patients with neglect performed on a somatosensory exploration task and also found evidence of two forms of deficit. One seemed to be body-centric, but the effect barely reached statistical significance; the other was mapped with respect to the “line of sight” and was more significant. It was not possible to distinguish whether the line of sight effect was due to a deficit in head-centric or retinotopic coordinates. The results of the present study would also be consistent with either a head-centric, retinotopic, or object centred deficit, but they do not support the hypothesis that neglect is body-centric.

I thank Professor C Kennard for useful comments and criticisms.

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A novel cytochrome P-450IID6 (CYP1D6) mutant gene associated with multiple system atrophy

PARKINSON’S disease and multiple system atrophy, including olivopontocerebellar atrophy and striatoniigral degeneration, are characterised by pathological changes in the brain, including the basal ganglia. Several neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and debrisoquine, can induce parkinsonism in animals. The poor metaboliser phenotype of debrisoquine hydroxylation was considered to be associated with susceptibility to Parkinson’s disease, and one genomic mutation (poor metaboliser genotype) of cytochrome P-450IID6 (CYP1D6), which metabolises debrisoquine and possibly also detoxifies MPTP and TiQ, has been reported to be overexpressed in Parkinson’s disease.

Furthermore, it was reported that a novel mutation from Arg26 to Cys26 located at the HhaI site in exon 6 of the CYP1D6 gene might be associated with Parkinson’s disease (the mutated allele frequency was 0.21). We have analysed the CYP1D6 gene according to the method of Tsunoe et al in 10 Japanese patients with multiple system atrophy (only sporadic cases; diagnostic criteria by Quinn) to investigate the relation between the polymorphism of CYP1D6 and susceptibility to multiple system atrophy. There was no significant difference in the frequency of the poor metaboliser genotype between the cases and controls (p > 0.05). As the table shows, however, the frequency of the HhaI site located at the HhaI site in exon 6 in the patients (0.45) was significantly higher than that in the controls (0.09) (p < 0.05).

These results suggest that the polymorphism of the HhaI site in exon 6 of the CYP1D6 gene may be a useful molecular marker for susceptibility to multiple system atrophy, as in Parkinson’s disease, and that both diseases may have a mutual pathogenetic association with similar defence against neurotoxic environmental factors. Further studies in a larger number of patients are necessary to confirm these preliminary findings.

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Genotypes of the HhaI site in the CYP1D6 gene from patients with multiple system atrophy and controls

<table>
<thead>
<tr>
<th>Wild type homozygote (n/a)</th>
<th>Heterozygote (n/a)</th>
<th>Mutant type homozygote (n/a)</th>
<th>Allode frequency (to/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with MSA 4</td>
<td>Controls 77</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*p < 0.05. Values are the numbers of patients and controls. MSA = multiple system atrophy.
Is visual neglect body-centric?

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