White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer’s disease, vascular dementia, and normal aging

R Barber, P Scheltens, A Gholkar, C Ballard, I McKeith, P Ince, R Perry, J O’Brien

Abstract

Objectives—Alzheimer’s disease and vascular dementia are associated with an increase in changes in white matter on MRI. The aims were to investigate whether white matter changes also occur in dementia with Lewy bodies and to examine the relation between white matter lesions and the cognitive and non-cognitive features of dementia with Lewy bodies, Alzheimer’s disease, and vascular dementia.

Methods—Proton density and T2 weighted images were obtained on a 1.0 Tesla MRI scanner in patients with dementia with Lewy bodies (consensus criteria; n=37, mean age=75.9 years), Alzheimer’s disease (NINCDS/ADRDAD; n=28, mean age=77.4 years), vascular dementia (NINDS/AIREN; n=25, mean age=76.8 years), and normal controls (n=26, mean age=76.2 years). Cognitive function, depressive symptoms, and psychotic features were assessed using a standardised protocol. Periventricular hyperintensities (PVHs), white matter hyperintensities (WMHs) and basal ganglia hyperintensities (BGHs) were visually rated blind to diagnosis using a semi-quantitative scale.

Results—Periventricular hyperintensities were positively correlated with age and were more severe in all dementia groups than controls. Total deep hyperintensities scores (WMHs plus BGHs) were significantly higher in all dementia groups than controls and higher in patients with vascular dementia than those with dementia with Lewy bodies or Alzheimer’s disease. In all patients with dementia, frontal WMHs were associated with higher depression scores and occipital WMHs were associated with an absence of visual hallucinations and delusions. Conclusion—In common with Alzheimer’s disease and vascular dementia, PVHs and WMHs were significantly more extensive in dementia with Lewy bodies than in controls. This overlap between different de- mencias may reflect shared pathological mechanisms. The link between frontal WMHs and depression and the absence of occipital WMHs and psychotic symptoms has important implications for understanding the neurobiological basis of these symptoms.

Keywords: dementia; white matter hyperintensities; Magnetic resonance imaging

Magnetic resonance imaging can detect hyper-intense white matter lesions, especially with proton density and T2 weighted scans. These changes can be divided into those immediately adjacent to the ventricles (periventricular hyperintensities; PVHs) and those located in the deep white matter (white matter hyperintensities; WMHs). Periventricular hyperintensities and WMHs probably result from different pathological processes and have been described in various conditions including normal aging, vascular dementia, and Alzheimer’s disease.

The prevalence, severity, and distribution of PVHs and WMHs seem to vary between different disorders and with age. Vascular dementia is associated with increased PVHs and WMHs compared with Alzheimer’s disease and age matched normal controls. Patients with Alzheimer’s disease also have more extensive PVHs than controls but there are conflicting findings in relation to WMHs. Bowen et al found that WMHs were increased in patients with Alzheimer’s disease compared with controls, Scheltens et al found an increase only in late onset patients although others have found no difference. Inconsistency between studies may be attributable to variation in scanning techniques, sample size and selection, and the rating scales used.

Dementia with Lewy bodies has been recently recognised as a major cause of dementia, clinically and neuropathologically distinct from Alzheimer’s disease and vascular dementia. It is probably the second commonest form of late life dementia, accounting for up to 20% of cases. Dementia with Lewy bodies is characterised by the triad of visual hallucinosis, fluctuating cognitive impairment, and parkinsonism. Pathologically, intracytoplasmic, neuronal inclusion bodies (Lewy bodies) are found in the neocortex, limbic cortex, subcortical nuclei, and brainstem. There have been few neuroimaging studies of dementia with Lewy bodies and changes in white matter on MRI in this disease have not previously been investigated.

The clinical importance of changes in white matter seen on MRI in dementia is poorly understood. There is growing evidence that changes in white matter are linked to depressive illness in late life and possibly psychotic symptoms in late onset schizophrenia.
While white matter lesions are involved in the pathogenesis of depressive and psychotic symptoms in dementias, the role is unclear. The aims of this study were to compare white matter changes on MRI in patients with dementia with Lewy bodies with those with Alzheimer’s disease, vascular dementia, and normal age-matched controls, and to examine their relation to cognitive and non-cognitive features of dementia. Our hypothesis was that, in common with Alzheimer’s disease and vascular dementia, an increased prevalence of changes in white matter would occur in dementia with Lewy bodies. We also tested the hypothesis that changes in white matter in late onset dementias are associated with depressive and possibly psychotic symptoms. A representative sample of community dwelling elderly subjects was included and white matter lesions were rated using a semiquantitative scale to record the prevalence, severity, and anatomical distribution of these changes.

Methods

SELECTION OF PATIENTS WITH DEMENTIA

Eighty patients over the age of 60 years who fulfilled DSM IV criteria for dementia were recruited. Seventy-five patients were obtained from a community dwelling population of patients referred to local old age psychiatry and geriatric medicine services for evaluation of possible dementia. Fifty patients were recruited from a dementia research clinic. The research was approved by the local ethics committee and all patients, as well as their nearest relative, gave informed consent.

ASSESSMENTS AND DIAGNOSIS

Diagnosis was made after a detailed clinical assessment. This included an interview with the subject and the most knowledgeable informant using the geriatric mental state/history aetiology schedule, review of clinical records, full psychiatric and medical history, and mental state and physical examination. A standard dementia screen was completed which included haematology and biochemistry analysis, thyroid function tests, syphilis serology, B12 and folate concentrations, and CT.

Standardised clinical diagnostic criteria were used to characterise the type of dementia. Diagnoses of Alzheimer’s disease, vascular dementia, and dementia with Lewy bodies were made in accordance with NINCDS/ADRDA, NINDS/AIREN and dementia with Lewy bodies consensus criteria respectively by consensus agreement between three experienced raters (JO’B, CB, IMcK). Diagnosis was made blind to MRI findings. Pathological confirmation of clinical diagnosis has since been acquired in four patients. Applying these criteria, 28 patients had Alzheimer’s disease (definite n=2, probable n=24, and possible n=2), 25 had vascular dementia (probable n=15 and possible n=10), and 27 had dementia with Lewy bodies (definite n=2, probable n=24, and possible n=1).

Within three months of completing MRI all patients underwent a further assessment. Cognitive function was measured using the Cambridge cognitive examination which incorporates the mini mental state examination (MMSE). Depressive symptoms were rated using the Montgomery and Asberg depression rating scale (MADRS) and a history of psychotic symptoms (delusions, misidentifications, auditory hallucinations, and visual hallucinations) since onset of dementia was recorded using the Columbia University scale for psychopathology in Alzheimer’s Disease (CUSPAD).

NORMAL CONTROLS

Twenty-six age-matched controls were recruited from among spouses and friends of patients with dementia. A detailed history and examination were undertaken to include demographic data and physical and psychiatric status. All control subjects completed the same assessments as listed above: CAMCOG, MMSE, MADRS, CUSPAD. Exclusion criteria were evidence of current depression (from history or MADRS>10) or dementia (from history or score<80 on the CAMCOG) and history of any other significant neurological, physical, or psychiatric disorder including drug and alcohol misuse.

MRI SCANNING PROTOCOL

All scans were performed on a 1.0 Tesla Siemens Magnetom Impact MRI scanner. Whole brain axial images of 5 mm thickness (0.5 mm gap) were obtained using proton density weighted and T2 weighted turbo fast spin echo sequences to allow detailed visualisation of white matter lesions (RARE technique-rapid acquisition with relaxation enhancement: TR=2800 ms; TE 14/85 ms; matrix 256×256; field of view=23 mm giving pixel size=0.92×0.92 mm; acquisition time=4 min 13s).

WHITE MATTER RATING

Using a standardised scale white matter lesions were rated from hard copies of proton density and T2 weighted turbo fast spin echo sequences. The scale provided a semiquantitative measurement of the type, size, frequency, and location of PVHs and WMHs, as shown in table 1. Hyperintensities were rated in five regions: frontal,
Con and DLB, Con and AD, VaD and DLB (p<0.001), and between VaD and DLB (p<0.05).

Table 3  Periventricular hyperintensities

<table>
<thead>
<tr>
<th></th>
<th>DLB (n=27)</th>
<th>AD (n=28)</th>
<th>VaD (n=25)</th>
<th>Con (n=26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bands</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>23 (85%)</td>
<td>28 (100%)</td>
<td>24 (96%)</td>
<td>19 (73%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Median score</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Frontal caps</td>
<td>25 (93%)</td>
<td>26 (93%)</td>
<td>24 (96%)</td>
<td>23 (89%)</td>
<td></td>
</tr>
<tr>
<td>Median score</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Occipital caps</td>
<td>22 (82%)</td>
<td>21 (75%)</td>
<td>20 (80%)</td>
<td>8 (31%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Median score</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total PVH</td>
<td>27 (100%)</td>
<td>28 (100%)</td>
<td>25 (100%)</td>
<td>24 (92%)</td>
<td>=0.001‡</td>
</tr>
<tr>
<td>Median score</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

For abbreviations see table 2.

Post hoc Mann-Whitney U test showed significant differences between:

*Con and VaD (p<0.05) and between Con and AD (p<0.01)
†Con and AD (p<0.001) and between Con and VaD (p<0.001)
‡Con and DLB (p<0.05) and between Con and VaD (p<0.001)
§Con and DLB, Con and AD, VaD and DLB (p<0.001), and between VaD and AD (p<0.01), and between VaD and Con (p<0.001)

temporal, parietal, occipital, and basal ganglia (BGH).

**STATISTICAL ANALYSIS**

The statistical package SPSS for Windows (Release 7.0) was used for data analysis. Differences between groups on continuous variables were assessed using analysis of variance (ANOVA) with post hoc Scheffé tests to determine group differences. For non-parametric data a Kruskal-Wallis test was used followed by a post hoc Mann-Whitney U test or Pearson χ² statistic as appropriate, with Fisher's exact probability test calculated for 2x2 tables when the expected cell frequency was <5. Associations between white matter lesions and clinical variables were examined using the Mann-Whitney U test or Spearman's rank order correlation coefficient (r) as appropriate. All statistical tests were two tailed and were regarded as significant at p<0.01 for correlations and p<0.05 for all other tests.

**Results**

**SUBJECT CHARACTERISTICS**

Subject characteristics are summarised in table 2. Groups were well matched for age, sex, history, and years of education. As would be expected, CAMCOG and MMSE scores were significantly lower in all dementia groups compared with controls (p<0.001). Patients with dementia with Lewy bodies were significantly more impaired than those with vascular dementia on MMSE (13.6 ± 18.2; p<0.05) and CAMCOG (46.1 ± 62.0; p<0.05).

There were no differences between dementia groups for MADRS scores although all dementia groups had significantly more depressive symptoms than controls (p<0.05). Patients with dementia with Lewy bodies experienced significantly more delusions (p<0.001), visual hallucinations (p<0.001), and auditory hallucinations (p<0.01) than those with Alzheimer's disease and vascular dementia.

**PERIVENTRICULAR HYPERINTENSITIES**

The results for PVHs are summarised in table 3. All dementia groups had significantly higher total PVH scores (sum of bands and caps) compared with controls (p<0.001). There were no significant differences between dementia with Lewy bodies, Alzheimer's disease, and vascular dementia, and overall PVHs were present in all dementia patients (100%) and nearly all age matched controls (92%).

Analysing bands and caps separately, periventricular bands were significantly more severe in patients with Alzheimer's disease (p<0.01) and vascular dementia (p<0.05) than in controls, and occipital caps were more severe (p<0.001) and frequent in all dementia groups compared with controls (dementia with Lewy bodies 82%, vascular dementia 80%, Alzheimer's disease 75% vs. controls 31%; p<0.001). By contrast, frontal caps were common to all groups (vascular dementia 96%, Alzheimer's disease 93%, dementia with Lewy bodies 92%, controls 89%).

Periventricular hyperintensities were positively correlated with age in all patients (total PVH score r=0.41, p<0.001) but were not associated with cognitive impairment or depressive and psychotic symptoms.

**WHITE MATTER AND BASAL GANGLIA HYPERINTENSITIES**

The results for WMHs and basal ganglia lesions are presented in table 4. Photographs of MRI demonstrating white matter changes in subjects from each group are shown in the figure.
Total deep hyperintensity scores (sum of the frontal, temporal, parietal, occipital, and basal ganglia scores) were significantly higher in all dementia groups compared with controls (vascular dementia median score=8 vs control median score=1, p<0.001; dementia with Lewy bodies median score=3, and Alzheimer's disease median score=4 vs control median score, p<0.05). Comparing the dementia groups, patients with vascular dementia had higher total lesion scores than those with Alzheimer's disease (p<0.01) and dementia with Lewy bodies (p<0.05). Overall, basal ganglia lesions were specifically associated with vascular dementia compared with all other groups (vascular dementia 68%, dementia with Lewy bodies 26%, Alzheimer's disease 21%, controls 12%; p<0.001).

A link between regional changes in white matter and specific non-cognitive symptoms in dementia patients was seen. The presence of frontal WMHs was associated with higher depression scores (mean MADRS score for patients with frontal WMHs =8.3 vs without =3.4; p<0.05). The presence of delusions (p<0.01) and visual hallucinations (p<0.05) was associated with the absence of occipital WMHs. No patient with delusions (n=34) had WMHs, and only one patient with visual hallucinations (n=29) had occipital WMHs. Auditory hallucinations showed a similar trend (p=0.06). White matter hyperintensity scores

Axial proton density MRI showing white matter lesions and ratings: (A) normal control (PVH score=0; WMH score=0); (B) patient with vascular dementia (PVH: frontal caps=2, occipital caps=2; WMH frontal=5, parietal=6); (C) patient with pathologically confirmed dementia with Lewy bodies (PVH: frontal caps=2, occipital caps=1; WMH frontal=2, parietal=3); (D) patient with pathologically confirmed Alzheimer's disease bodies (PVH: frontal caps=2, occipital caps=2; WMH frontal=6, parietal=6).
did not correlate with age or cognitive impairment.

Discussion
This is the first study to examine the presence of changes in white matter on MRI in dementia with Lewy bodies. The inclusion of patients with Alzheimer’s disease and patients with vascular dementia allowed comparison of changes in white matter between the three major types of late life dementia. Periventricular hyperintensities and WMHs were found to occur often in patients with dementia with Lewy bodies, Alzheimer’s disease, vascular dementia, and aged matched normal controls. These changes were, however, significantly more extensive in the dementia groups compared with controls.

The major strengths of this study include the recruitment of a representative community sample of elderly patients with late life dementia, well matched for age, sex, education, and duration of illness. Brain MRI was acquired using a standardised protocol, and changes in white matter were assessed blind by an experienced rater using a validated scale which provided detailed information on the frequency, size, and location of lesions. A potential criticism of this study is the reliance on clinical, rather than pathological, diagnoses. However, clinical diagnosis were made after detailed assessments and in accordance with standardised criteria. In the case of dementia with Lewy bodies, we have shown that the clinical criteria have a high specificity (0.95) indicating few false positive clinical diagnoses.22 A recent clinicopathological validation of current clinical criteria for dementia with Lewy bodies found a similar level of specificity (1.00), but low sensitivity (0.22), for the consensus diagnosis of probable dementia with Lewy bodies.22 Overall the clinical criteria seem to have a high positive predictive value for pathology of dementia with Lewy bodies itself, although the diagnosis does not exclude the possibility of mixed disease.22 The profile of patients with dementia with Lewy bodies studied conformed well with other published cohorts.23 Pathological confirmation of diagnosis has since been acquired in four patients (dementia with Lewy bodies n=2; Alzheimer’s disease n=2).

Periventricular Hyperintensities
Periventricular hyperintensities were found in all patients with dementia and 92% of controls. Previous reports have found PVHs to occur in 44% to 100% of patients with Alzheimer’s disease, 70% to 100% with vascular dementia, and 8% to 92% of elderly controls.1 3 In common with other studies,6 11 34-36 a positive correlation between the PVHs and age was also found. The high prevalence of PVHs in this study may therefore reflect, in part, the age of patients.

As found previously, PVHs were more severe in dementia patients than in controls.6 18 However, not all PVHs were equal in this regard. Bands and occipital caps, by contrast with frontal caps, were more severe and common in dementia groups than in controls.

The near ubiquitous presence of frontal caps lends further support to the notion that they occur as a normal, age related change.6 18 Histologically, frontal PVHs probably result from areas of demyelination and astrocytic gliosis.10

Divergence in the severity of periventricular bands and occipital caps between demented and non-demented patients suggests that pathological processes contribute to their development. The convergence of results within the dementia groups would argue in favour of a common pathogenesis. Interestingly, Fazekas et al25 found that patients with Alzheimer’s disease had significantly more PVHs than controls but that this association was not independently linked to the disease; rather it seemed to be related to atrophy as measured by ventricular enlargement. Other studies have also found an association of PVHs and atrophy,24 and in vitro pathological studies indicate that PVHs are associated with loss of the ependymal lining, demyelination, and gliosis.42 43 Damage to the integrity of the ependymal lining may in turn result in abnormal dynamics of CSF and increased water content.34 42 43 Histological studies of PVHs in dementia with Lewy bodies are necessary to establish whether similar changes occur.

The absence of a link between PVHs and the clinical features of dementia with Lewy bodies was consistent with negative reports involving non-demented elderly patients, patients with Alzheimer’s disease, and patients with vascular dementia.2 The relation between PVHs seen on MRI and clinical features remains unclear. Perhaps, as some authors have suggested, MRI is more sensitive at detecting PVHs, but CT is more specific and detects lesions which are more tightly coupled with pathological change and outcome.22

White Matter and Basal Ganglia Hyperintensities
White matter hyperintensities also occurred often in all groups and differences between demented and non-demented patients largely resulted from variations in the severity and distribution of lesions. The pattern of WMHs in dementia with Lewy bodies was broadly similar to Alzheimer’s disease, but less extensive than vascular dementia. The prevalence of WMHs in vascular dementia and Alzheimer’s disease conformed well with previous studies, which have detected WMHs in up to 100% of patients with vascular dementia7 22 and between 60%-100% of patients with Alzheimer's disease.7

The pathological correlates of WMHs in dementia with Lewy bodies have not yet been determined. The similar pattern of hyperintensities in dementia with Lewy bodies and Alzheimer’s disease suggests that they may share a convergence in white matter pathology. White matter lesions in Alzheimer’s disease have been linked to ischaemic changes9 but histological findings from other studies have identified various abnormalities, including dilated perivascular spaces, arteriosclerosis, partial loss of myelin and axons, gliosis, lacunar
infarcts, and congenital diverticula. Clearly not all WMHs result from ischaemic damage and postmortem examination, ideally preceded by postmortem brain MRI, is necessary to determine the nature of white matter pathology in dementia with Lewy bodies. In vivo characterisation of WMHs using proton magnetic resonance spectroscopy may also provide useful pathological and diagnostic information.

The pronounced increase of basal ganglia lesions in vascular dementia is consistent with previous reports and suggests that these changes may be useful as a diagnostic aid in the differential diagnosis of vascular dementia from dementia with Lewy bodies as well as Alzheimer’s disease. Interestingly, the lack of an association between dementia with Lewy bodies and basal ganglia hyperintensities indicates that these lesions are unlikely to contribute to the development of parkinsonism in dementia with Lewy bodies.

There are contrasting reports on the association between changes in white matter and cognitive function. Discrepancies may be explained by methodological differences. In common with many other studies, the rating of white matter lesions in this study was not volumetric. Semi-quantitative rating scales may not be sufficiently sensitive to detect correlations with cognition unless sample size is large. By contrast, positive correlations have been reported with moderate sample sizes using volumetric measures. In addition, in healthy patients a “threshold” effect has been reported such that cognitive deficits only become evident beyond a certain severity of changes in white matter. Longitudinal studies might provide further insights into the nature of any interaction between WMHs, cognitive function, and disease progression.

Non-cognitive features of dementias occur commonly and are clinically important. There is growing evidence that frontal and subcortical WMHs are implicated in late life depression and influence outcome, possibly by disruption of frontal-subcortical circuits. WMHs are implicated in late life depression and imply a common pathophysiology of depression irrespective of diagnosis.

The association of psychotic symptoms with specific brain abnormalities in dementias remains controversial. Howicz et al. studied patients with Alzheimer’s disease and found that hallucinations were associated with cerebral atrophy and enlarged third ventricles but not abnormalities in white matter, though they did not examine regional changes in white matter. In this study, there was a negative association between occipital WMHs and psychosis which was not explained by group differences between dementia with Lewy bodies (who hallucinate a lot) and other groups (who hallucinate less). This findings could imply that a “disease” free occipital lobe, presumably with abnormalities located in other brain regions, is necessary to develop psychosis, and that disruption of neural circuits involving visual association areas might prevent hallucinations. Using functional MRI Howard et al. have suggested that visual hallucinations are, at least in part, located in the primary visual cortex, raising the possibility that strategically located lesions in white matter may disrupt this process. Whether occipital WMHs might suppress visual hallucinations is clearly an area which requires further investigation.

Conclusion
Periventricular hyperintensities were found to be common in dementia with Lewy bodies as well as Alzheimer’s disease, vascular dementia, and aged matched controls, but were uniformly more severe in all major types of dementia compared with controls. This could indicate that PVHs result from a common pathogenesis, possibly related to brain atrophy. The pattern of deep hyperintensities in dementia with Lewy bodies was broadly similar to Alzheimer’s disease and both groups showed modest increases in the severity of changes in white matter compared with controls. Overall WMHs and basal ganglia lesions were most pronounced in patients with vascular dementia. A link between the presence of frontal WMHs and depression and the absence of occipital WMHs and psychotic symptoms was found. This has important implications for understanding the neurobiological basis of these symptoms.

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