Carotid sinus syndrome is common in dementia with Lewy bodies and correlates with deep white matter lesions

R A Kenny, F E Shaw, J T O’Brien, P H Scheltens, R Kalaria, C Ballard

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Background: Carotid sinus syndrome (CSS) is a common cause of syncope in older persons. There appears to be a high prevalence of carotid sinus hypersensitivity (CSH) in patients with dementia with Lewy bodies (DLB) but not in Alzheimer’s disease.

Objective: To compare the prevalence of CSH in DLB and Alzheimer’s disease, and to determine whether there is an association between CSH induced hypotension and brain white matter hyperintensities on magnetic resonance imaging (MRI).

Methods: Prevalence of CSH was compared in 38 patients with DLB (mean (SD) age, 76 (7) years), 52 with Alzheimer’s disease (80 (6) years), and 31 case controls (73 (5) years) during right sided supine carotid sinus massage (CSM). CSH was defined as cardioinhibitory (CICSH; >3 s asystole) or vasodepressor (VDCSH; >30 mm Hg fall in systolic blood pressure (SBP)). T2 weighted brain MRI was done in 45 patients (23 DLB, 22 Alzheimer). Hyperintensities were rated by the Scheltens scale.

Results: Overall heart rate response to CSM was slower (RR interval = 3370 ms (640 to 9400)) and the proportion of patients with CICSH greater (32%) in DLB than in Alzheimer’s disease (1570 (720 to 7900); 11.1%) or controls (1600 (720 to 3300); 3.2%) (p<0.01)). The strongest predictor of heart rate slowing and CSH was a diagnosis of DLB (Wald 8.0, p<0.005). The fall in SBP during carotid sinus massage was greater with DLB (40 (22) mm Hg) than with Alzheimer’s disease (30 (19) mm Hg) or controls (24 (19) mm Hg) (both p<0.02). Deep white matter hyperintensities were present in 29 patients (64%). In DLB, there was a correlation between magnitude of fall in SBP during CSM and severity of deep white matter changes (R=0.58, p=0.005).

Conclusions: Heart rate responses to CSM are prolonged in patients with DLB, causing hypotension. Deep white matter changes from microvascular disease correlated with the fall in SBP. Microvascular pathology is a key substrate of cognitive impairment and could be reversible in DLB where there are exaggerated heart rate responses to carotid sinus stimulation.

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Carotid sinus syndrome (CSS) is characterised by exaggerated heart rate and blood pressure responses to carotid sinus stimulation—bradycardia and hypotension. The syndrome manifests clinically as dizziness, syncope, and falls. It is virtually exclusively a diagnosis of aging and is rarely diagnosed before age 50 years. The prevalence increases with advancing age. The afferent neural input from the carotid sinus is through the glossopharyngeal nerve. The reflex is modulated at the cardiovascular centre in the brain stem. Cardiovascular reflex efferent pathways are through the vagus nerve and the sympathetic nerves. The bradycardic component of CSS reflects exaggerated heart rate slowing mediated by vagal innervation of the sinus node and the atrioventricular node. The hypotension is caused by acute withdrawal of sympathetic innervation to the peripheral vasculature. The underlying cause of the syndrome is unknown. In the context of cardiovascular syncope, CSS is the attributable cause in up to 20% of older patients.

Carotid sinus hypersensitivity is diagnosed when these exaggerated heart rate or blood pressure responses are present in people who have not experienced syncope. The prevalence in asymptomatic healthy elderly people is 0–12%. The natural history of carotid sinus hypersensitivity is not known.

Symptoms such as falls and syncope caused by the bradycardic component can be treated successfully by cardiac pacing. To date, treatment strategies for the vasodepressor component have been less successful.

Dementia is becoming progressively more important as the population ages and the consequent burden of health care and costs increase. Five per cent of over 65s and 20% of over 80s suffer from dementia. Alzheimer’s disease accounts for approximately 60% of cases, and dementia with Lewy bodies (DLB) for a further 20%. We have observed in our clinical practice that carotid sinus hypersensitivity is common in patients with dementia, particularly those with DLB. This clinical observation was supported by recent pilot data.

A high prevalence of carotid sinus hypersensitivity in DLB is consistent with prominent cholinergic deficits particular to DLB which could theoretically predispose to some of the parasympathetically mediated heart rate abnormalities of carotid sinus hypersensitivity. Conversely, recent data have confirmed cardiac sympathetic denervation in DLB patients which was not evident in Alzheimer’s disease or controls, and such denervation is consistent with unopposed, and thus exaggerated, parasympathetic activity.

The incidence of falls in patients with dementia is fivefold that of the general older population and is particularly high.

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Abbreviations: ADRDA, Alzheimer’s Disease and Related Disorders Association; BGH, basal ganglia hyperintensity; CICSH, cardioinhibitory carotid sinus hypersensitivity; CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; CSS, carotid sinus syndrome; DLB, dementia with Lewy bodies; DWMH, deep white matter hyperintensity; MMSE, mini-mental state examination; NINCDS, National Institute of Neurological and Communicative Disorders; PVH, periventricular hyperintensity; VDCSH, vasodepressor carotid sinus hypersensitivity.
in patients with DLB.\textsuperscript{26} If the prevalence of the brady-
arrhythmic component CICSH is high, it may offer an
important option for therapeutic intervention for the
prevention of falls in dementia—symptoms which have
hitherto been notoriously difficult to treat.

Hyperintense lesions detected by magnetic resonance
imaging (MRI) often occur in elderly patients, especially
those with dementia.\textsuperscript{28} They include periventricular (PVH),
basal ganglia (BGH), and deep white matter hyperintensities
(DWMH). Correlative neuropathological studies have sug-
gested that DWMH are the result of microvascular pathol-
ogy.\textsuperscript{29} This is consistent with evidence that hypertension is a
key risk factor. Although less studied, episodic hypotension,
with associated hypoperfusion, may also be important.\textsuperscript{30} Such
episodes are common in patients with carotid sinus
hypersensitivity. Microvascular pathology as a key substrate
of cognitive impairment has been emphasised in recent
reports.\textsuperscript{31} On the basis of previous preliminary observations,\textsuperscript{32}
it is therefore likely that carotid sinus hypersensitivity—
which results in repeated hypotensive episodes—will be
associated with more severe microvascular pathology.

We hypothesised that carotid sinus hypersensitivity is more
prevalent in patients with DLB than in Alzheimer’s dementia,
and that the magnitude of the fall in systolic blood pressure
during carotid sinus massage is associated with the severity
of white matter hyperintensities on MRI.

METHODS
Clinical sample
The prevalence of carotid sinus hypersensitivity in patients
with DLB was compared with the prevalence in Alzheimer’s
patients and non-demented case controls. Consecutive
dementia patients seen by old age psychiatrists within the
Institute for Ageing and Health in Newcastle upon Tyne, UK,
were recruited from the dementia case register. Patients had
a detailed clinical assessment, including a standardised
history\textsuperscript{33} (history and aetiology schedule), a cognitive assess-
ment (mini-mental state examination, MMSE),\textsuperscript{34} and a
physical examination (including the modified unified
Parkinson’s disease rating scale, UPDRS).\textsuperscript{35} The clinical
diagnosis of DLB was made using the consensus criteria\textsuperscript{36}
and probable Alzheimer’s disease was diagnosed using the
NINCDS-ADRDA system.\textsuperscript{30} For the first 50 cases from the
series coming to necropsy, the positive predictive values were
95\% for DLB and 80\% for Alzheimer’s disease against the
necropsy diagnosis.\textsuperscript{37} Only cases of probable DLB and
Alzheimer’s disease were included. Cases of possible
Alzheimer’s disease, possible DLB, or vascular dementia were
excluded. Patients taking acetylcholinesterase drugs were
also excluded.

Case controls who had no history of falls or syncope during
the previous three years and who had an MMSE score of $\geq 27$
were recruited from poster advertising in outpatient clinics.
The study was approved by the Newcastle ethics commit-
tee, and informed consent was obtained from participants or
from informants.

Cardiovascular assessment
All study participants had neurological and cardiovascular
assessments including full clinical examination, resting 12
lead surface ECG, and heart rate and blood pressure
responses to right supine carotid sinus stimulation.

Carotid sinus stimulation was carried out after 10 minutes
of supine rest, in a quiet laboratory, in the mornings between
0900 and 1100 hours. Phasic blood pressure (measured by the
non-invasive, continuous technique of digital photoplethys-
mography; Finapres, Ohmeda) and continuous heart rate (12
lead surface ECG, 25 mm paper speed) were recorded during,
and for two minutes after, carotid sinus massage. Firm
massage was carried out over the right carotid sinus for five
seconds. The carotid sinus location was the point of
maximum pulsation of the carotid artery, two finger breadths
below the angle of the jaw and level with the thyroid cartilage
border.\textsuperscript{12,33}

Contraindications to carotid sinus massage included recent
myocardial infarction (within three months), recent transient
ischaemic episode or stroke (within three months), and any
history of ventricular fibrillation.\textsuperscript{38,39}

Cardioinhibitory or mixed carotid sinus hypersensitivity
(CICSH) was defined as three seconds or more of asystole
with or without an associated vasodepressor response, and
vasodepressor carotid sinus hypersensitivity as a fall of
30 mm Hg or more in systolic blood pressure in patients in
whom the heart rate response was less than three seconds.\textsuperscript{4}

Current prescriptions were recorded for each patient. Drugs
were classified according to whether they were known to
cause or exaggerate bradycardia or hypotension.\textsuperscript{37}

Neuroimaging
MRI was done using a 1.0 Tesla Siemens scanner. Axial
whole brain images of 5 mm thickness were obtained using
proton density weighted and T2 weighted turbo/fast spin echo
sequences to allow detailed visualisation of periventricular,
depth white matter, and basal ganglia hyperintensities, rated
on the Scheltens scale,\textsuperscript{40} which produces a composite
measure of severity based upon the number, size, and
distribution of lesions, by an expert rater (PS), blind to the
results of the cardiovascular assessment. Significant periven-
tricular hyperintensities were defined as $\geq 2$; significant deep
white matter intensities were defined as $\geq 1$; and significant
basal ganglia hyperintensities were defined as $\geq 1$, as defined
in a preliminary publication.\textsuperscript{25}

Statistics
A comparison between subjects with Alzheimer’s disease
and DLB was the primary aim of the research. Each group was
compared separately with control subjects. This applies to all
variables analysed. As two primary comparisons were under-
taken, a significance of 2.5\% rather than 5\% was adopted.

Continuous variables (age, blood pressure) were plotted to
check for outliers and wildly skewed distributions. The
distribution of data was normal with the exception of RR
interval responses to carotid sinus massage.

Statistics are reported as mean (SD) for all comparisons,
with the exception of RR interval response to carotid sinus
massage, which was reported as median (extreme range).

Other comparisons were evaluated as secondary analyses.
As other factors such as age, sex, blood pressure, and
cardiovascular drug treatment have previously been reported
as associations of carotid sinus hypersensitivity, an additional
analysis was undertaken when significant differences were
identified using logistic regression.

For continuous variables such as age and blood pressure,
pairwise comparisons between groups were made using an
independent sample t test, and for binary variables (such as
sex) pairwise comparisons were made using a $\chi^2$ test. For the
MRI evaluations, the partial correlations (controlling for age)
of PVH, BGH, and DWMH with fall in systolic blood pressure
during carotid sinus massage were evaluated with using
Pearson’s R. Evaluations were undertaken with the SPSS
computerised statistics package (version 9).\textsuperscript{41}

RESULTS
Ninety patients with dementia were recruited (52 with
Alzheimer’s disease and 38 with DLB), along with 31 case
controls. No participants had contraindications to carotid
sinus massage. Both Alzheimer and DLB patients were older than
controls and the Alzheimer patients were older than
controls.
Table 1  Demographic details and resting systolic and diastolic recordings in patients with dementia with Lewy bodies, Alzheimer’s disease, and case controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>DLB</th>
<th>AD</th>
<th>Control</th>
<th>AD v DLB</th>
<th>AD v Control</th>
<th>DLB v AD</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>38</td>
<td>52</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age [years]</td>
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<td>80</td>
<td>73</td>
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<td>0.01</td>
<td>0.000</td>
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<tr>
<td>Female [%]</td>
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<td>31</td>
<td>12 (39)</td>
<td>0.59</td>
<td>0.21</td>
<td>0.07</td>
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<tr>
<td>MMSE</td>
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<td>17</td>
<td>14</td>
<td>0.462</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SBP (mm Hg)</td>
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<td>139</td>
<td>147</td>
<td>0.453</td>
<td>0.074</td>
<td>0.206</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>72</td>
<td>74</td>
<td>83</td>
<td>0.466</td>
<td>0.004</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) unless stated.
AD, Alzheimer’s disease; DBP, diastolic blood pressure; DLB, dementia with Lewy bodies; MMSE, mini-mental state examination; SBP, systolic blood pressure.

Comorbidity did not differ for dementia subtypes or case controls. No participants had previous stroke, five had treated hypertension (two DLB, one Alzheimer, two controls), two had diabetes mellitus (one DLB, one control), four had symptoms of ischaemic heart disease (two Alzheimer, two controls), one DLB patient had chronic obstructive airways disease, two cases had epilepsy (one DLB, one control), and six had heart failure (two DLB, two Alzheimer, two controls).

The prescription of cardiovascular drugs known to cause or exacerbate bradycardia or hypotension was also similar in all groups:

- DLB: diuretics (4), isosorbide (1), nifedepine (1), prazosin (1);
- Alzheimer’s disease: digoxin (1), diltiazem (1), isosorbide (2);
- Controls: ACE inhibitors (1), diuretics (2), isosorbide (2) and nifedepine (1).

No patients were taking antiparkinsonism drugs.

Cardiovascular responses

All patients were in sinus rhythm. Resting systolic blood pressures were similar for DLB, Alzheimer’s disease, and controls (table 1). Resting diastolic blood pressures were significantly lower in dementia patients (73, (17) mm Hg) than in the controls (83 (15) mm Hg; p<0.004), but did not differ for dementia subtypes.

In DLB patients the overall heart rate slowing during carotid sinus massage was significantly longer than in either Alzheimer patients (p<0.001) or controls (p<0.001). The number of patients with CICSH was also greater in DLB—31.5% had CICSH, compared with 11.3% in the Alzheimer group (p<0.02) and 3.2% in the controls (p<0.003). Both the degree of heart rate slowing and the frequency of CICSH were similar for Alzheimer patients and controls. The overall fall in SBP during carotid sinus massage (table 2) was more marked in DLB than in Alzheimer’s disease (p<0.017) or case controls (p<0.002); this most probably reflects the slower heart rates in DLB in response to carotid sinus massage, because the prevalence of VDCSH did not differ for Alzheimer’s disease (38.4%), DLB (26%), or case controls (36.6%) when patients with CICSH were excluded from the analyses.

When using a stepwise logistic regression analysis to explore the relative influences of risk factors on the diagnosis of CICSH, the only variable selected was the diagnosis of DLB (Wald 6.3, p<0.001). Other variables were age (Wald 1.1, p = 0.29), sex (Wald 0.8, p = 0.37), SBP (Wald 3.1, p = 0.08), DBP (Wald 0.1, p = 0.78), and cardiovascular drugs (Wald 0.3, p = 0.59).

MRI data

Forty five patients (23 DLB, mean (SD) age, 75 (6.4) years, MMSE 17.2 (4.6), 44% female; 22 Alzheimer’s disease, mean age 78.6 (3.9) years, MMSE 17.9 (4.4), 60% female) had MRI scans. Mean RR interval was 2200 ms (920 to 8720) in DLB and 1200 ms (800 to 7800) in Alzheimer’s disease; average fall in SBP during carotid sinus massage was 40 mm Hg (18 to 53) in DLB and 33 mm Hg (0 to 88) in Alzheimer’s disease. Nineteen (42.2%) of the patients had significant basal ganglia hyperintensities (BGH), 29 (64.4%) had significant deep white matter changes (DWMH), and 43 (96%) had significant periventricular hyperintensities (PVH). The severity of DWMH was greater in DLB patients than in Alzheimer patients (6.5 (0.94) v 3.9 (3.1); t = 2.1, p = 0.04) but PVH and BGH did not differ between DLB and Alzheimer’s disease: PVH, 3.2 (1.3) v 3.3 (1.0); t = 0.1, p = 0.91; BGH, 0.96 (1.49) v 0.53 (0.94); t = 1.0, p = 0.30.

Seventeen patients (38%) had CICSH and 26 (58%) had VDCSH. In DLB patients there was a significant association between the magnitude of fall in blood pressure and the severity of DWMH, and a trend towards an association with BGH, but no relation with the severity of PVH. No significant associations were evident between the length of the RR interval after carotid sinus massage and any of the categories of hyperintense lesion. In the Alzheimer patients (n = 22) there were no significant associations between hyperintense lesions and either the magnitude of blood pressure fall or the prolongation of RR interval (table 3). There was no evidence in the DLB cases that systolic blood pressure, diastolic blood pressure, age, or MMSE were confounding factors.

DISCUSSION

Patients with DLB were more likely to have CICSH and overall had much more marked slowing of heart rate and a more marked fall in systolic blood pressure in response to carotid sinus massage than either patients with Alzheimer’s disease or normal age matched controls. Neither the prevalence of CICSH, the degree of heart rate slowing, nor the fall in SBP during carotid sinus massage differed between Alzheimer patients and controls. Although the control subjects were younger than the dementia patients, the magnitude of the difference in prevalence of CICSH is unlikely to be explained by an average age difference of five years. Indeed, the diagnosis of DLB was independently associated with CICSH and with the extent of heart rate slowing and the fall in systolic blood pressure when other variables which differed between the groups, such as age, were considered. These findings present important and previously unrecognised options for the possible treatment...
of falls in DLB, which require further study in a prospective series.

It is now well recognised that cardiovascular disorders—in particular CICSH—can cause falls in non-demented older adults.37 38 The reasons for this are twofold. First, up to 30% of patients with syncope have amnesia for loss of consciousness and only recall falling.40 Given that an eye witness account of patients with syncope have amnesia for loss of consciousness of falls in DLB, which require further study in a prospective series. The reasons for this are twofold. First, up to 30% of patients with syncope have amnesia for loss of consciousness and only recall falling.40 Given that an eye witness account of patients with syncope have amnesia for loss of consciousness.
of Lewy body pathology in effector organs such as the cardiac conducting system and the peripheral nerves or vasculature is not yet known.  

The bradycardiac response to carotid sinus massage is entirely mediated by the vagus nerve and is abolished by moderate doses of atropine. Acetylcholinesterase treatments can be expected to exaggerate the bradycardiac response. Syncope after the use of acetylcholinesterase inhibitors has been reported. Our group has recently described a case of carotid sinus syndrome which was unmasked by the use of acetylcholinesterase inhibitors. In that case, a cardiac pacemaker was implanted to control symptoms of falls and syncope, and the patient was able to resume acetylcholinesterase treatment without further adverse events. Given the high prevalence of CICSH in DLB, it may be that patients with this condition should be screened for carotid sinus hypersensitivity in advance of starting acetylcholinesterase inhibitors. Prospective studies of carotid sinus hypersensitivity in patients receiving acetylcholinesterase inhibitors are now important, given the proven benefit of these agents in patients with DLB.  

Vasodepressor responses, independent of heart rate slowing (VDCSCH), are attributed to acute withdrawal of peripheral sympathetic activity to capacitance vessels and arterial vasculature in response to carotid sinus stimulation. The number of patients with VDCSCH was similar for all groups but the overall fall in systolic blood pressure in response to carotid sinus massage was most exaggerated in DLB. These systolic blood pressure differences are a result of the more exaggerated heart rate slowing in DLB patients, and are thus amenable to control by cardiac pacing.

The reason why there was no association between deep white matter changes and the degree of heart rate slowing is not clear, unless the numbers were insufficient to show a difference. However, there was a significant association with the degree of hypotension during carotid sinus massage and DWMH in DLB patients. The greater severity of DWMH in the DLB group is consistent with our hypothesis that carotid sinus hypersensitivity may contribute to these MRI changes because this phenomenon is more frequent in DLB.  

Although carotid sinus massage is a crude method for diagnosing carotid sinus hypersensitivity, it is the best one available for identifying the patients who are most likely to benefit from cardiac pacing in its favour, it is a simple technique that can be applied without the need for sophisticated equipment or expertise, and it is thus a valuable screening tool for application to a prevalent disorder. In nondemented older adults, neurological complication rates from the procedure are 0.4%. There are no data on the incidence of neurological complications during carotid sinus massage in patients with dementia. To date, most reported neurological complications have occurred during carotid sinus massage carried out with the patient upright. We therefore electrolyte the study to examine the prevalence of carotid sinus hypersensitivity with the patient supine. There were no complications, so we recommend this procedure for screening for carotid sinus hypersensitivity in patients with dementia until more information is available about complication rates in this population.

The association between DWMH and a fall in systolic blood pressure during carotid sinus massage in DLB patients supports our hypothesis that a sudden drop in blood pressure resulting from carotid sinus stimulation is an important potential substrate of white matter pathology, consistent with recent reports indicating that orthostatic hypotension is a risk factor for DWMH. The absence of an association in Alzheimer’s disease is probably a reflection of the less dramatic falls in blood pressure in that condition compared with DLB. The Schelten’s scale is a well validated visual rating instrument for white matter hyperintensities that is more sensitive to change than other scales.

There is accumulating evidence that white matter and basal ganglia hyperintensities are associated with cognitive impairment, especially tests of fronto-executive function, both in demented and non-demented subjects. It is possible that white matter hyperintensities contribute to cognitive dysfunction in patients with DLB. It should also be considered that brain stem pathology may be the substrate of CICSH in DLB—for example, in multisystem atrophy there is a reported association between autonomic failure and catecholaminergic neurones in the ventrolateral medulla. Furthermore, it is well recognized that Lewy body pathology is prominent in the key brain stem areas where cardiovascular control is also modulated. These possible associations require further study.

Conclusions

The extent of both carotid sinus induced heart rate slowing and hypotension is significantly exaggerated in DLB. The degree of hypotension correlates with deep white matter changes and possibly with basal ganglia hyperintensities. These findings may have important implications for successful treatment of falls in some DLB patients, and for screening before starting acetylcholinesterase treatment. They need to be tested in prospective intervention trials.

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