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

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 7800); 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.

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%. If 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.
in patients with DLB.\(^{26}\) If the prevalence of the bradyarrhythmic 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.

Hypertensive lesions detected by magnetic resonance imaging (MRI) often occur in elderly patients, especially those with dementia.\(^{26}\) They include periventricular (PVH), basal ganglia (BGH), and deep white matter hyperintensities (DWMH). Correlative neuropathological studies have suggested that DWMH are the result of microvascular pathology.\(^{27}\) This is consistent with evidence that hypertension is a key risk factor. Although less studied, episodic hypotension, with associated hypoperfusion, may also be important.\(^{28}\) 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.\(^{29}\) On the basis of previous preliminary observations,\(^{25}\) it is therefore likely that carotid sinus hypersensitivity—which results in repeated hypertensive 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 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\(^{26}\) (history and aetiology schedule), a cognitive assessment (mini-mental state examination, MMSE),\(^{27}\) and a physical examination (including the modified unified Parkinson’s disease rating scale, UPDRS).\(^{28}\) The clinical diagnosis of DLB was made using the consensus criteria\(^{29}\) and probable Alzheimer’s disease was diagnosed using the NINCDS-ADRDA system.\(^{30}\) 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.\(^{11}\) 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 acetycholinesterase 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 committee, 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 photoplethysmography; 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.\(^{12-13}\)

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.\(^{24-26}\)

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.\(^{1}\)

Current prescriptions were recorded for each patient. Drugs were classified according to whether they were known to cause or exaggerate bradycardia or hypotension.\(^{27}\)

#### 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, deep white matter, and basal ganglia hyperintensities, rated on the Scheltens scale;\(^{38}\) 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 periventricular 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.\(^{25}\)

#### 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 undertaken, 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).\(^{39}\)

### 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...
DLB patients. Sex distribution was similar for patients and controls. Cognitive function (MMSE) was similar for DLB and Alzheimer patients (table 1).

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 11.5% 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 in response to carotid sinus stimulation 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. The reasons for this are twofold. First, up to 30% of patients with syncope have amnesia for loss of consciousness and only recall falling. Given that an eye witness account of patients with syncope have amnesia for loss of consciousness. The reasons for this are twofold. First, up to 30% of series.

of syncope is not universal in moderate to severe dementia. Thus a drop in balance instability are so common. We have not correlated the abnormal haemodynamic responses described in this cross sectional series with prospective data on fall rates. Nonetheless, the consequences of the neurological abnormalities in DLB are likely to be exaggerated by such intermittent and profound changes in heart rate and blood pressure. It is our view that a study of cardiac pacing intervention to modify falls in DLB is now timely.

The reason for the high prevalence of carotid sinus hypersensitivity in DLB is present speculative. It may be related to the presence of Lewy body pathology at the sites where the reflex is relayed in the brain stem. Afferent impulses from the carotid sinus and aortic arch baroreflexes are modulated at the nucleus tractus solitarius, from whence heart rate and blood pressure responses are mediated through the vagal and sympathetic nerves. Equally, it may be that reflex control from higher centres is abnormal because of DLB related neuropathological or neurochemical changes. Involvement of effector organs is also a possibility. Studies of cardiac innervation using MIBG scans confirm peripheral sympathetic denervation in DLB, which is not evident in Alzheimer’s disease or controls. Cardiac sympathetic denervation would facilitate dominance of cardiac vagal responses consistent with CICSH. The extent

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<tr>
<td>Fall in SBP during CSM (mm Hg)</td>
<td>40 (22)</td>
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<td>Number with CICSH</td>
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<tr>
<td>Number with VDCSH</td>
<td>10/26 (38%)</td>
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<tr>
<td>Fall in SBP in subjects without CICSH (mm Hg)</td>
<td>38 (19)</td>
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For continuous variables (age and blood pressure), pairwise comparisons between groups were made using an independent sample t test, and for binary variables pairwise comparisons were made using a Z test. A Mann–Whitney U test was used for comparison of RR interval response.

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of Lewy body pathology in effector organs such as the cardiac conducting system and the peripheral nerves or vasculature is not yet known.42 The bradyarrhythmic response to carotid sinus massage is entirely mediated by the vagus nerve and is abolished by moderate doses of atropine.3 Acetylcholinesterase treatments can be expected to exaggerate the bradyarrhythmic response. Syncope after the use of acetylcholinesterase inhibitors has been reported.41 Our group has recently described a case of carotid sinus syndrome which was unmasked by the use of acetylcholinesterase inhibitors.44 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.45

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.46 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.3 5 7 47

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.3 5 7 47 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 non-sophisticated equipment or expertise, and it is thus a valuable screening tool for application to a prevalent disorder. 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. Further evidence that DLB is prominently affected by this phenomenon is 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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