

Cerebral emboli as a potential cause of Alzheimer's disease and vascular dementia: case-control study

Nitin Purandare, Alistair Burns, Kevin J Daly, Jayne Hardicre, Julie Morris, Gary Macfarlane, Charles McCollum

Abstract

Objective To compare the occurrence of spontaneous cerebral emboli and venous to arterial circulation shunts in patients with Alzheimer's disease or vascular dementia and controls without dementia.

Design Cross sectional case-control study.

Setting Secondary care old age psychiatry services, Manchester.

Participants 170 patients with dementia (85 with Alzheimer's disease, 85 with vascular dementia) and 150 age and sex matched controls. Patients on anticoagulant treatment, patients with severe dementia, and controls with marked cognitive impairment were excluded.

Main outcome measures Frequencies of detection of spontaneous cerebral emboli during one hour monitoring of the middle cerebral arteries with transcranial Doppler and venous to arterial circulation shunts by a transcranial Doppler technique using intravenous microbubbles as an ultrasound contrast.

Results Spontaneous cerebral emboli were detected in 32 (40%) of patients with Alzheimer's disease and 31 (37%) of those with vascular dementia compared with just 12 each (15% and 14%) of their controls, giving significant odds ratios adjusted for vascular risk factors of 2.70 (95% confidence interval 1.18 to 6.21) for Alzheimer's disease and 5.36 (1.24 to 23.18) for vascular dementia. These spontaneous cerebral emboli were not caused by carotid disease, which was equally frequent in dementia patients and their controls. A venous to arterial circulation shunt indicative of patent foramen ovale was found in 27 (32%) Alzheimer's disease patients and 25 (29%) vascular dementia patients compared with 19 (22%) and 17 (20%) controls, giving non-significant odds ratios of 1.57 (0.80 to 3.07) and 1.67 (0.81 to 3.41).

Conclusion Spontaneous cerebral emboli were significantly associated with both Alzheimer's disease and vascular dementia. They may represent a potentially preventable or treatable cause of dementia.

Introduction

Vascular risk factors are implicated in both Alzheimer's disease and vascular dementia, but the underlying pathophysiology remains uncertain.¹ Both Alzheimer's disease and vascular dementia are associated with carotid atherosclerosis.² A large embolus may cause stroke or transient ischaemic attack, but repeated small asymptomatic emboli over many months or years may also cause progressive cerebral damage. Carotid disease is one potential source of spontaneous cerebral emboli (SCE). Valvular heart disease, atrial fibrillation, and paradoxical embolisation of venous emboli into the arterial circulation are other potential sources of

SCE.³⁻⁴ Atrial fibrillation has been shown to be a risk factor for dementia,⁵ and paradoxical embolisation is associated with cryptogenic stroke in young adults, postoperative confusion after hip replacement, migraine, decompression sickness in scuba divers, and transient global amnesia.⁶⁻⁹

We standardised a transcranial Doppler technique to detect venous to arterial circulation shunts (v-aCS) and did a pilot study in patients with Alzheimer's disease or vascular dementia.¹⁰⁻¹¹ SCE and v-aCS were more common in dementia patients than in community controls. We set up this study to explore definitively the frequencies of SCE, carotid artery disease, and v-aCS in Alzheimer's disease and vascular dementia.

Methods

A case-control study with patients with Alzheimer's disease or vascular dementia matched to controls of the same sex and age.

Study subjects

We recruited patients with dementia through a network of old age psychiatrists in Greater Manchester. We matched controls to dementia patients by sex, age, and geographical area of residence. Based on the mini-mental state examination,¹² we excluded patients with severe dementia and controls with significant cognitive impairment. We excluded patients and controls who were taking anticoagulant drugs.

Study assessments

We collected details on cardiovascular risk factors at interview with patients and their carers or with controls. We examined the psychiatric notes to verify medical and psychiatric history for cases. An independent clinician diagnosed Alzheimer's disease and vascular dementia.¹³⁻¹⁴ Vascular technologists independently investigated SCE, carotid disease, and v-aCS; they were not told the diagnosis but could not be fully blinded to dementia.

Spontaneous cerebral emboli—We detected SCE by continuous transcranial Doppler insonation of the middle cerebral arteries through the transtemporal window for one hour. This was done before transcranial Doppler investigation of v-aCS, to avoid detecting air microemboli. We used international consensus criteria to define emboli.¹⁵

Carotid artery disease—We used ultrasound to image carotid disease and used established criteria to calculate the severity of stenosis.¹⁶

Editorial by
Kivipelto and
Solomon

Department of
Psychiatry,
University of
Manchester,
Manchester
Nitin Purandare
*senior lecturer in old
age psychiatry*
Alistair Burns
*professor of old age
psychiatry*

Academic Surgery
Unit, University of
Manchester
Kevin J Daly
lecturer in surgery
Jayne Hardicre
study coordinator
Charles McCollum
professor of surgery

South Manchester
University Hospitals
NHS Trust,
Manchester
Julie Morris
*head of medical
statistics*

School of
Epidemiology and
Health Sciences,
University of
Manchester,
Manchester
M13 9PT

Gary Macfarlane
*professor of
epidemiology*

Correspondence to:
G Macfarlane
cmcc@
manchester.ac.uk

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Table 1 Spontaneous cerebral emboli (SCE)

Detection of SCE	Alzheimer's disease		Vascular dementia		All dementia	
	Cases (n=80)	Controls (n=80)	Cases (n=83)	Controls (n=83)	Cases (n=167)	Controls (n=145)
No (%) SCE positive*	32 (40)	12 (15)	31 (37)	12 (14)	65 (39)	21 (15)
Odds ratio (95% CI); P value	3.22 (1.52 to 6.81); 0.002		4.80 (1.83 to 12.58); 0.001		3.76 (2.15, 6.57); <0.001	
Adjusted odds ratio (95% CI); P value	2.70 (1.18 to 6.21); 0.019†		5.36 (1.24 to 23.18); 0.025‡		3.46 (1.84, 6.52); <0.001‡	

*Numbers of case-control pairs corresponding to presence/absence of SCE: Alzheimer's disease +/+ (n=3), -/- (n=39), +/- (n=29), -/+ (n=9), discordance rate=48%; vascular dementia +/+ (n=7), -/- (n=47), +/- (n=24), -/+ (n=5), discordance rate=35%.

†Adjusted for cardiovascular risk factors (significant at 10% level) in table 3.

‡Adjusted for age, sex, and cardiovascular risk factors (significant at 10% level) in table 3 on bmj.com.

Detection of venous to arterial circulation shunts—We used a standardised transcranial Doppler technique to detect v-aCS, with insonation of the middle cerebral arteries and intravenous injection of an emulsion of air microbubbles in saline as an ultrasound contrast medium (see bmj.com).¹⁷⁻¹⁹ Two trained vascular technologists counted microbubble embolic signals from the middle cerebral arteries. A blinded study coordinator verified the results by analysis of data tapes. We based the criteria for “significant” v-aCS on our previous study (see bmj.com).¹⁰

Statistical analysis

We used logistic regression analysis to compare dementia patients with their matched controls for cardiovascular risk factors, the occurrence of SCE, carotid disease, and v-aCS. We assessed the relation between SCE positivity and cardiovascular risk factors.

Results

We recruited a total of 170 patients with dementia (85 with Alzheimer's disease and 85 with vascular dementia) and 150 controls. The mean age difference between cases and controls was 0.12 (SD 1.74) years (see bmj.com).

Risk factors for cardiovascular disease

Patients with Alzheimer's disease and vascular dementia had a similar profile of cardiovascular risk factors to their respective controls (see bmj.com), except for the more frequent history of stroke or transient ischaemic attack in vascular dementia patients compared with their controls (odds ratios 8.5 (95% confidence interval 2.0 to 36.8) for stroke and 21.5 (5.2 to 88.7) for transient ischaemic attack). Compared with Alzheimer's disease patients, those with vascular dementia were more likely to have a history of stroke ($P < 0.001$), transient ischaemic attack ($P < 0.001$), antiplatelet drugs ($P < 0.001$), and hypertension ($P = 0.01$) and lower high density lipoprotein cholesterol concentrations ($P = 0.03$).

Spontaneous cerebral emboli

In a single hour of transcranial Doppler monitoring, we detected SCE in 32 (40%) Alzheimer's disease and 31 (37%) vascular dementia patients compared with 12 (15%) and 12 (14%) respectively of their controls (table 1). After exclusion of participants reported in the pilot study, the odds ratio was 2.88 (1.29 to 6.43) for Alzheimer's disease (61 case-control pairs, 26 (43%) v 11 (18%), $P = 0.01$) and 4.00 (1.50 to 10.66) for vascular dementia (70 case-control pairs, 27 (38%) v 12 (17%), $P = 0.006$). The odds ratios for SCE (all participants) remained similar and highly significant at 2.70 (1.18 to 6.21) for Alzheimer's disease and 5.36 (1.24 to

23.18) for vascular dementia after adjustment for cardiovascular risk factors.

Carotid disease

We detected moderate or severe (>50%) carotid stenosis in 7/82 (8%) Alzheimer's disease patients and 20/78 (26%) vascular dementia patients compared with 13/82 (16%) and 26/78 (20%) of their respective controls ($P = 0.14$ and $P = 1.0$). We detected severe (>70%) carotid stenosis in none of the Alzheimer's disease patients, 6 (8%) vascular dementia patients, and 5 (6%) of both sets of controls ($P = 0.06$ and $P = 0.74$).

Venous to arterial circulation shunts

We detected a “significant” v-aCS in 27 (32%) Alzheimer's disease patients and 25 (29%) vascular dementia patients compared with 19 (22%) and 17 (20%) of their respective controls. Excluding participants reported in the pilot study gave odds ratios of 1.58 (0.77 to 3.26) for Alzheimer's disease (64 case-control pairs, 23 (36%) v 16 (25%), $P = 0.21$) and 1.50 (0.72 to 3.11) for vascular dementia (72 case-control pairs, 22 (31%) v 16 (22%), $P = 0.28$).

SCE and cardiovascular risk factors

SCE were associated with all the major cardiovascular risk factors in controls (table 2). We found no such association in dementia patients, implying that SCE may be universal in dementia. We found a greater than 70% carotid stenosis in 4 (19%) of 21 SCE positive controls compared with only 6 (5%) of 124 controls who were SCE negative ($P = 0.02$), but the difference was not significant in patients with dementia. SCE were not significantly associated with v-aCS in either patients or controls.

Discussion

Spontaneous cerebral emboli were significantly more common in patients with dementia than in age and sex matched population controls. The frequency of SCE was similar in Alzheimer's disease and vascular dementia, which may explain the similarity in risk factors between these two dementias with differing final pathology.²⁰

Frequency and sources of SCE

SCE may occur in carotid disease; with several hours of monitoring, SCE can be detected in more than half of patients with >70% stenosis.^{21 22} As we found no significant association between carotid disease and SCE in dementia patients, carotid atherosclerosis seems to be an unlikely source for most SCE in dementia. None of the study participants had clinically significant or uncontrolled atrial fibrillation, and we excluded everyone taking anticoagulant drugs. Undiagnosed atrial fibrillation would not explain the

Table 2 Comparison of spontaneous cerebral emboli (SCE) positive and SCE negative participants. Values are numbers (percentages) unless stated otherwise

Characteristic	Dementia*			Controls		
	SCE positive (n=65)	SCE negative (n=102)	P value	SCE positive (n=21)	SCE negative (n=124)	P value
Mean (SD) age (years)	76.7 (7.8)	76.0 (6.6)	0.53	76.5 (6.8)	76.5 (6.5)	1.0
Male sex	37 (57)	51 (50)	0.38	9 (43)	69 (56)	0.28
Mean (SD) MMSE score	21.1 (4.4)	21.9 (5.1)	0.29	28.2 (1.6)	28.6 (1.4)	0.21
Carotid disease:						
>50%	10 (15)	15 (15)	0.90	8 (38)	23 (19)	0.06
>70%	3 (5)	2 (2)	0.32	4 (19)	6 (5)	0.023
Venous to arterial circulation shunt:						
“Significant”	22 (34)	29 (28)	0.46	4 (19)	28 (23)	0.72
“Major”	11 (17)	18 (18)	0.90	2 (10)	16 (13)	0.66
Mean (SD) blood pressure (mm Hg):						
Systolic	143.1 (26.0)	140.9 (27.8)	0.62	150.5 (24.4)	143.6 (22.9)	0.22
Diastolic	74.3 (14.3)	76.8 (13.1)	0.26	86.0 (11.9)	77.4 (14.5)	0.013
Mean (SD) lipid concentrations (mmol/l):						
Cholesterol	5.42 (1.23)	5.27 (0.99)	0.39	5.32 (1.13)	5.41 (1.06)	0.73
HDL cholesterol	1.37 (0.39)	1.34 (0.40)	0.66	1.39 (0.33)	1.42 (0.49)	0.80
LDL cholesterol	3.34 (1.05)	3.14 (0.80)	0.17	3.03 (1.05)	3.20 (0.91)	0.45
Triglycerides†	1.36 (0.9-1.9)	1.45 (1.0-1.9)	0.37	1.62 (1.2-2.2)	1.63 (1.1-2.3)	0.94
MI or angina:						
MI	4 (6)	8 (8)	0.68	3 (14)	9 (7)	0.28
Angina	9 (14)	13 (13)	0.81	6 (29)	17 (14)	0.09
Stroke or TIA:						
Stroke	7 (11)	11 (11)	1.0	5 (24)	3 (2)	0.001
TIA	18 (28)	33 (32)	0.52	6 (29)	6 (5)	<0.001
PVD	16 (25)	21 (21)	0.54	7 (33)	26 (21)	0.22
Diabetes	3 (5)	7 (7)	0.55	2 (10)	5 (4)	0.28
Smoking (current)	9 (14)	18 (18)	0.66	2 (10)	18 (15)	0.79
Antiplatelet drugs	29 (45)	42 (41)	0.66	12 (57)	32 (26)	0.004

HDL=high density lipoprotein; LDL=low density lipoprotein; MI=myocardial infarction; MMSE=mini-mental state examination; PVD=peripheral vascular disease; TIA=transient ischaemic attack.

*Alzheimer's disease or vascular dementia.

†Geometric mean (interquartile range).

presence of emboli in almost 40% of dementia patients.

We found the expected association between cardiovascular risk factors and SCE in controls. In dementia, SCE were much more common and were not associated with cardiovascular risk factors. Other mechanisms such as inflammation could be involved in the pathophysiology of both SCE and dementia.

Are some SCE paradoxical?

Our study was not sufficiently powered to conclude that any real difference existed in the frequencies of “significant” venous to arterial circulation shunt (patent foramen ovale) between patients with dementia and controls. Percutaneous closure of patent foramen ovale is used increasingly for atrial septal aneurysms or after multiple embolic events. The risks and benefits of this procedure are also being explored in other conditions, such as migraine, and in divers.²³

Limitations

A possible limitation of our study was that vascular technologists could not be blinded to the case or control status of participants. This is unlikely to have biased our results, as we recorded transcranial Doppler sessions for subsequent blind analysis. We were also unable to compare data on health between participants and non-participants (those who refused consent). Although we asked about memory problems, controls did not have neuropsychological assessment to exclude early dementia.

Cardiovascular risk factors

The distribution of cardiovascular risk factors was similar in dementia patients and their controls. Only a history of stroke or transient ischaemic attack was more common in vascular dementia than in controls and Alzheimer's disease patients. The likely explanation is that a history of cerebrovascular symptoms and infarcts on brain imaging would influence the clinician to diagnose vascular dementia rather than Alzheimer's disease. As the diagnosis of vascular dementia would usually lead to the prescription of antiplatelet drugs, this factor was also associated with vascular dementia.

This study is the first to show an association between SCE and dementia. The similar frequency of emboli in both types of dementia suggests a common cause and shared pathophysiology.

Conclusion

Spontaneous cerebral emboli were significantly more frequent in both Alzheimer's disease and vascular dementia patients than in sex and age matched controls. They may be a potentially preventable or treatable cause of dementia.

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What is already known on this topic

Considerable overlap exists between Alzheimer's disease and vascular dementia

Vascular risk factors may be involved in the causation of both conditions

Spontaneous cerebral emboli are associated with increased risk of stroke and cognitive impairment in patients having carotid or cardiac surgery

What this study adds

Spontaneous cerebral emboli are significantly associated with both Alzheimer's disease and vascular dementia and may be involved in the pathophysiology of both conditions

Spontaneous cerebral emboli may represent potentially preventable or treatable cause of both types of dementia

Ethical approval: Local research ethics committees in Manchester and Stockport: South and North Manchester LREC reference SOU/98/132; Central Manchester LREC reference CEN/00/027/CA; Stockport LREC reference EE/SR/MREC2029.

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Effects of armed conflict on access to emergency health care in Palestinian West Bank: systematic collection of data in emergency departments

Maren Johanne Heilskov Rytter, Anne-Lene Kjældgaard, Henrik Brønnum-Hansen, Karin Helweg-Larsen

National Institute of Public Health, Øster Farimagsgade 5A, 1399 DK, Copenhagen, Denmark

Maren Johanne Heilskov Rytter
medical student

Anne-Lene Kjældgaard
medical student

Henrik Brønnum-Hansen
senior researcher
Karin Helweg-Larsen
senior researcher

Correspondence to: K Helweg-Larsen
khl@niph.dk

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Abstract

Objective To assess the impact of restrictions in access to hospital services imposed on the civilian population during the armed conflict in the Palestinian territories occupied by Israel.

Design Consecutive registration of demographic and medical data, with information about transportation time, delay in access to hospital, and course of hospital contact.

Setting Three hospital emergency departments in Bethlehem and Nablus, in the occupied Palestinian West Bank, during one week in each hospital.

Participants All patients seeking health care in the three hospitals during the study period.

Results A total of 394 of the 2228 emergency department contacts reported being delayed at checkpoints or by detours on their way to the emergency department. Hospital admission was significantly more common for these patients: 32% (n = 125) compared with 13% (n = 205) among those who were not delayed.

Conclusion 18% of the emergency department contacts were delayed because of the occupation. The higher hospital admission rate in this group suggests that restrictions in access to hospital services influence the severity of the medical conditions presented.

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