ORIGINAL RESEARCH

Effect of vascular burden as measured by vascular indexes upon vascular dementia: a matched case-control study

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Background: Vascular dementia (VaD) is a challenging illness that affects the lives of older adults and caregivers. It is unclear how multiple vascular risk factor exposures (polyvascular disease) affect VaD.

Purpose: To determine the relationship between multiple vascular risk exposures, as counted on an index in cases with VaD, compared with healthy age-/gender-matched controls.

Methods: This was a matched case-control study of subjects living in Olmsted County, MN with documented VaD. Controls were selected by gender and age within 3 years from those who did not have dementia. The exposures included a total index (eleven exposure factors) added together, along with indexes for cerebrovascular disease (two exposures), cardiovascular disease (four exposures), vascular disease (three exposures), and lifestyle (two exposures). Analysis used matched conditional univariable logistic regression for each index.

Results: A total of 1736 potential subjects were identified, and 205 subjects were diagnosed with VaD. There was a significant association of the total score index with an odds ratio of 1.45 (95% confidence interval 1.21–1.74). The cerebrovascular index was also associated with VaD with an odds ratio of 12.18 (95% confidence interval 6.29–23.61). The cardiovascular and vascular indexes were also associated with VaD status. The lifestyle index was not associated with VaD.

Conclusion: The cumulative role of multiple vascular risk factors or diseases increased the risk of VaD, as noted by the total vascular index. The lifestyle index did not reveal any significant differences. Further work is required for evaluation of these indexes.

Keywords: polyvascular disease, elderly, vascular dementia

Introduction

Vascular dementia (VaD) is a common condition that affected the lives of 594,000 people in the US in 2007.[1] This number will grow as the population ages and as individuals live longer lives with vascular disease. VaD has two primary components – namely, cerebrovascular disease and cognitive decline with neurological deficits.[2] Many assume the risk factors for VaD are the same as for stroke.[3] This may not be true. The risk factors for VaD in the community are still not completely known, and there is some controversy over some traditional vascular risk factors such as smoking[4] and hypertension.[5] Although the individual risk factors still face controversy, one important entity that has not been fully explored is polyvascular disease. Polyvascular disease is the accumulation of multiple vascular diseases or risk factors, including the addition of coronary artery disease and peripheral artery disease. Individuals often have more than one vascular risk factor and can possess more than

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27

one type of vascular disease. One might hypothesize that the increase in vascular risk factor burden, or the increase in the number of vascular diseases, could potentially increase the risk of VaD.

In looking at stroke, a relationship between the number of strokes and the risk of VaD has been demonstrated.[6] The continued burden of vascular insults upon the brain with multiple strokes increases risk for future dementia. What is not clear is the role of multiple risk factors upon the development of VaD. Do multiple risk factors or vascular diseases beyond the cerebrovascular system increase the risk of developing VaD? We hypothesize that an increase in the absolute number of risk factors will increase the risk of VaD. To address and answer this question we conducted a matched case-control study of individuals in Olmsted County, MN with documented VaD and controls without VaD.

Methods
Study design
This study utilized a retrospective matched case-control analysis of patients living within Olmsted County. The specific design and cohort have previously been described.[7] The study was reviewed and approved by the Mayo Clinic Institutional Review Board. The principles of the research followed the Declaration of Helsinki.[8]

Setting
All cases and controls in the study received care at the Mayo Clinic in Olmsted County. The Mayo Clinic is the largest health care provider in Olmsted County. The cases and controls were obtained from the time period of 1994–2002. The timeline of the comorbid medical exposures occurred any time prior to the index date of diagnosis or matching.

Participants/cases
The investigators identified cases as patients with a clinically documented diagnosis of definite VaD. The cases were determined from the inpatient and outpatient medical care records from 1994 to 2002. Personnel from the Mayo Clinic's Health Science Research Department initially screened the electronic medical record for any one of the 40 diagnoses suggestive of dementia. The diagnostic information to make the determination of VaD was obtained from the medical history, neuroimaging studies, and clinical diagnosis from the medical record. The authors diagnosed VaD based upon the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Ensignement en Neurosicences (NINDS-AIREN) criteria for definite VaD.[2]

Investigators using NINDS-AIREN criteria have had moderate to good agreement in determining VaD.[9]

Controls
Controls were drawn and matched from the same general cohort as the cases. They were matched using the criteria described in the following section and had exposures evaluated from the index date of the aforementioned matched control.

Exclusion criteria
Potential controls with the diagnosis of dementia from any cause prior to the index date were excluded from the study. Cases or controls that refused record review in accordance with Minnesota state law were also excluded from the study.

Matching
Cases were identified and matched 1:1 by age (±2 years), gender, and their Mayo Clinic registration number. The controls were matched on age, due to the known effect of age upon the development of dementia.[10] Matching by a registration number serves as a proxy for the amount of potential medical care previously received within the Mayo Clinic's system, and this medical information is linked to the medical record.[11] Matching age and the medical clinic number gives a similar length of medical care.

Population of Olmsted County
The US Census estimated Olmsted County's population to be 124,277 in 2000 during the time of recruitment.[12] Individuals in Olmsted County possessed a higher educational level of 38.9% with a bachelor degree, compared with 27.4% in the US. The demographic picture in Olmsted County reflected the following: 90.3% white, 4.3% Asian, and 2.7% black or African American.[12]

Exposure variables
Each exposure variable was counted singly to determine whether it was present in the cases or controls. To determine the vascular burden, the indexes were created. These indexes were not weighted and included all variables.

Demographic and lifestyle exposure variables
Age and gender were collected and matched for cases and controls. Educational years were determined based on the last year of education the subject attended. The lifestyle outcome variables were tobacco use ever, alcohol use ever,

and obesity. A dichotomous answer of yes or no was used for tobacco use. For the alcohol use, the comparisons were made in a similar manner with a yes or no answer. Educational years and tobacco and alcohol use were obtained by self-report from the subject prior to the index date of case or control determination. Obesity was defined as a body mass index of >30 kg/m^2 using the National Heart, Lung, and Blood Institute's definition of obesity.[13] If the subject had a measured body mass index >30 kg/m^2 in the preceding 10 years, the subject was considered obese.

Comorbid health conditions

There were eight primary vascular comorbid medical conditions that were considered for the indexes. Cerebrovascular disease was defined by the presence of two major comorbid illnesses of a previous stroke and/or transient ischemic attacks (TIAs). Cardiovascular risk factors included a diagnosis of myocardial infarction (MI), a history of anginal chest pain, a history of atrial fibrillation, and a diagnosis of congestive heart failure (CHF). The final two risk factors were hypertension and diabetes. Hypertension was defined by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII criteria as systolic blood pressure >140 mmHg.[14] Systolic blood pressure was measured in the office by the clinical staff.

All information on both cases and controls were abstracted directly from the medical record, including physician notes, laboratory data, letters, and non-visit care information. These sources of information also included all information on hospitalizations and dismissal diagnoses from the hospital and outpatient clinic. The clinical team made the diagnosis while caring for the subject. The details of the Mayo Clinic medical record and how it was used in the study are noted in our previous manuscript.[7] All information was abstracted by trained nurses, who were blinded to the study hypothesis. The information was subsequently recorded on an electronic spreadsheet (Excel, Redmond, WA). All of the exposures were classified as yes or no in a dichotomous fashion.

Cumulative index evaluation

After the aforementioned demographic, lifestyle, and comorbid exposure variables were collected, we created five different indexes to evaluate the potential role of all the risks together (total index), as well as specific indexes of lifestyle, cerebrovascular, cardiovascular, and vascular. These indexes were created based upon the common risk factors for stroke[15] and by including the common vascular and coronary artery disease risk factors. The answers were summed and reported as a continuous number to represent increasing vascular burden. The indexes are as follows:

- Lifestyle index: addition of history of "ever smoking," "ever alcohol," and obesity (score 0–3)
- Cerebrovascular index: addition of history of stroke and history of TIA (score 0–2)
- Cardiovascular index: addition of history of CHF, angina, atrial fibrillation, and MI (score 0–4)
- Vascular risk index: addition of history of "ever tobacco," diabetes, and "ever hypertension" (score 0–3)
- Total index: addition of history of the following: "ever tobacco," "ever alcohol," obesity, stroke, TIA, CHF, angina, atrial fibrillation, MI, diabetes, and hypertension (score 0–11).

Data analysis

Simple descriptive statistics were calculated for demographic and comorbid medical illness data in the whole cohort, as well as in the cases and controls. The matching criteria were analyzed using a comparison between age and gender for cases and controls using parametric or nonparametric techniques as needed. The primary method of comparison between cases and controls utilized an odds ratio (OR) with 95% confidence intervals (CI). The authors analyzed the data using conditional logistic regression for the matched case-control data. Statistical testing was carried out at the conventional two-tailed significance level of $\alpha = 0.05$, corrected for multiple comparisons as appropriate.

Results
Demographics

The initial characteristics of the cohort have been described previously.[7] Briefly, 1736 potential subjects were identified using the initial evaluation from the medical record. After a review of the medical record, investigators identified 205 cases of VaD, which were matched and paired with controls for 205 pairs. The 205 pairs included 121 pairs who were female and 84 pairs who were male. The overall mean age in the cohort was 81.9 years (standard deviation [SD] 7.79 years). The average educational achievement was 12.3 years (SD 3.25 years). The full demographic and descriptive information of the overall cohort is noted in Table 1.

The ORs for the individual components of the indexes reveal the largest ORs for cerebrovascular disease. Stroke had the highest OR of 20.00 (95% CI 8.81–45.41), with TIAs having the second-highest OR of 5.90 (95% CI 3.02–11.53). Atrial fibrillation and diabetes were the only other comorbid medical conditions to have a significantly higher OR of

Table 1 Demographic overview of cases of VaD and controls in 205 matched pairs

	Overall (n = 410)	VaD cases (n = 205)	Controls (n = 205)
Demographic			
Male (%)	168 (41.0)	84 (41.0)	84 (41.0)
Age in years (SD)	81.9 (7.79)	82.1 (7.73)	81.6 (7.85)
Education in years (SD)	12.3 (3.25)	12.0 (3.35)	12.6 (3.13)
Body mass index kg/m^2 (SD)	26.2 (5.02)	25.8 (4.50)	26.5 (5.40)
Obese Y/N (%)	175 (53.4)	76 (51.4)	99 (55.0)
Lifestyle			
Ever alcohol use (%)	394 (76.9)	149 (74.9)	154 (79.0)
Ever tobacco use (%)	223 (55.5)	112 (55.7)	111 (55.2)
Comorbid health conditions			
History of stroke (%)	148 (37.0)	133 (65.8)	15 (7.6)
History of TIA (%)	80 (20.0)	66 (32.7)	14 (7.1)
History of CHF (%)	88 (21.8)	60 (29.3)	28 (14.1)
History of angina (%)	130 (32.2)	70 (34.1)	60 (30.3)
History of atrial fib (%)	88 (21.8)	58 (28.3)	30 (15.1)
History of previous MI (%)	78 (19.3)	41 (20.0)	37 (18.6)
History of hypertension (%)	291 (72.9)	161 (80.1)	130 (65.7)
History of diabetes (%)	101 (24.7)	64 (31.2)	37 (18.1)

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Abbreviations: CHF, congestive heart failure; fib, fibrillation; MI, myocardial infarction; SD, standard deviation; TIA, transient ischemic attack, VaD, vascular dementia.

exposure in the cases compared with the controls. The ORs for all of the exposures are noted in Table 2.

The ORs for the cumulative index scores for all of the indexes were statistically significant, except the lifestyle index. A majority of the indexes were statistically significant, in spite of the generally insignificant findings for the individual exposure variables. The OR of the total score index was 1.45 (95% CI 1.21–1.74). This index took into account all of the exposure variables. The index with the largest OR was the cerebrovascular index with an OR of 12.18 (95% CI 6.29–23.61). The OR of the cardiovascular index was 1.39

(95% CI 1.14–1.70), and the vascular index had a similar OR. The full findings of the five indexes are noted in Table 3.

Discussion

This study sought to determine the relationship between increasing numbers of vascular risk factors and the presence of VaD. We found that as a subject suffered an increasing number of vascular risks and comorbid illnesses, the risk of possessing VaD increased. The risk of VaD increased by 45% for each additional factor, using the total risk index. Thus, the risk of VaD almost doubled for every two vascular

Table 2 Univariable exposure odds ratios for cases of vascular dementia compared with controls in 205 matched pairs

	Odds ratio	95% CI	*P*-value
Lifestyle			
Obese Y/N	0.72	0.42–1.23	0.23
Ever alcohol use	0.80	0.49–1.31	0.38
Ever tobacco use	1.00	0.66–1.52	1.00
Comorbid health conditions			
History of stroke	20.00	8.81–45.41	<0.001*
History of TIA	5.90	3.02–11.53	<0.001*
History of CHF	1.08	0.62–1.89	0.78
History of angina	1.22	0.79–1.88	0.38
History of atrial fib	2.50	1.44–4.32	0.001*
History of previous MI	1.11	0.66–1.87	0.69
History of hypertension	0.87	0.59–1.29	0.49
History of diabetes	2.00	1.26–3.17	0.003*

Note: *Indicates significant value.
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Abbreviations: CHF, congestive heart failure; CI, confidence interval; fib, fibrillation; MI, myocardial infarction; TIA, transient ischemic attack.

Table 3 Univariate analysis of five different cumulative indexes for 205 matched pairs of vascular dementia cases and healthy controls

	Odds ratio	Lower 95% CI	Upper 95% CI	P-value
Cumulative index				
Lifestyle index[a]	0.82	0.61	1.11	0.20
Cerebrovascular index[b]	12.18	6.29	23.61	<0.001*
Cardiovascular index[c]	1.39	1.14	1.7	0.0013*
Vascular index[d]	1.50	1.16	1.94	0.0022*
Total score index[e]	1.45	1.21	1.74	<0.001*

Notes: [a]Lifestyle index; risk factors of (1) ever tobacco, (2) ever alcohol, (3) obesity (score 0–3); [b]cerebrovascular index; risk factors of (1) history of stroke, (2) history of TIA (score 0–2); [c]cardiovascular index; risk factors of (1) history of congestive heart failure, (2) history of angina, (3) history of atrial fibrillation, (4) history of myocardial infarction (score 0–4); [d]vascular index; risk factors of (1) ever tobacco, (2) history of diabetes, (3) history of hypertension (score 0–3); [e]total score index; risk factors of (1) ever tobacco, (2) ever alcohol, (3) obesity, (4) history of stroke, (5) history of transient ischemic attacks, (6) history of congestive heart failure, (7) history of angina, (8) history of atrial fibrillation, (9) history of myocardial infarction, (10) history of diabetes, (11) history of hypertension (score 0–11). *Significant.
Abbreviations: CI, confidence interval; TIA, transient ischemic attack.

illnesses or exposures. This was the important finding of our study. These findings are impressive and novel because they can potentially help a clinician to risk-stratify a patient for the development of VaD. Of the individual indexes, cerebrovascular disease had the highest OR at 12.18 (95% CI 6.29–23.61). The relationship between stroke and VaD would be expected, given the diagnostic criteria for VaD.[16] In previous studies, there was also a relationship between cerebrovascular symptoms and cognitive decline, as seen with the large population-based third National Health and Nutrition Examination Survey.[17] The important findings of a vascular load of risk factors are of particular importance in patients without a diagnosis of stroke or TIA.

The relationship between a functional index or a combination of risk factors and VaD has been reported in a small number of studies. The Charlson Comorbidity Index[18] has been evaluated in older adults with VaD and other forms of dementia, specifically Alzheimer's disease (AD). In patients with AD, there were increased risks of previous hospitalizations and fractures with increased comorbid medical illness in patients with AD, compared with a matched control.[19] In a separate study, a group of patients with cognitive decline tended to have more chronic health problems than people with intact memory.[20] Comparing the comorbid status of patients with VaD compared with AD or mixed dementia is also important. Patients with VaD were sicker than AD patients and had more comorbid illness and lower functional status.[21] The frailty index proposed by Rockwood and Mitnitski[22,23] is largely based on the accumulation of multiple comorbid diseases. As patients developed more diseases, the patient's functional status started to decline. Thus, indirectly, patients with vascular disease have more comorbid illnesses and are likely to be frailer than others without VaD. The comorbid illnesses discussed previously are largely nonspecific and do not necessarily reflect polyvascular disease. Our study is

unique because it specifically targets vascular illnesses and risk factors. However, the concepts may be similar, with an increase in comorbid conditions or vascular risk factors leading to an increase in the frequency of VaD.

The initial combinations of other vascular risks beyond cerebrovascular disease, including cardiovascular and vascular, did reveal that these measures have some association with VaD. The association of vascular illness and VaD goes beyond the cerebrovascular system. Of the individual risk factors, atrial fibrillation had the highest risk of VaD with an OR of 2.50 (95% CI 1.44–4.32). Atrial fibrillation has had an association with dementia in previous studies.[24,25] In spite of the remaining three cardiovascular risk factors being nonsignificant statistically, the cardiovascular index was significant with an OR of 1.39 (95% CI 1.14–1.70). Thus, the cumulative effect of cardiovascular disease is shown. In a similar fashion, the vascular index had a significant relationship with VaD, with diabetes as the only individually significant exposure variable. The lifestyle index did not show an association with VaD cases. This may reflect the opposite effects of smoking and alcohol use and also reflects a lack of significance of the individual components of the index. These indexes have not been validated on a population-based cohort and may merit future studies to develop scoring systems that can be applied to identify high-risk older adults at risk for developing VaD.

The concept of polyvascular disease is important for clinicians to consider. Patients face vascular diseases in not only the area of concern like the heart but also the cerebrovascular system and the rest of the body. The concept that multiple vascular beds are affected by a common genetic, lifestyle, and exposure process has been emerging. In the REACH (Reduction of Atherothrombosis for Continued Health) study, 77% of patients had single vascular comorbidity (coronary artery disease, cerebrovascular disease, vascular disease)

and 22.8% had polyvascular disease (more than one). The subjects with polyvascular disease had higher rates of cardiovascular death/nonfatal MI/nonfatal stroke with an OR of 1.63 (95% CI 1.45–1.83).[26] The role of polyvascular disease and the development of VaD still remain to be fully answered. The results of the REACH study shed some light on the role of multiple vascular illnesses or risks with the development of VaD. The results of our study are novel; however, they fit within the theme of multiple vascular illnesses having a higher risk of major vascular events.

There are multiple strengths of this study design and approach, which enhance its utility in determining the role of multiple vascular illnesses for the development of VaD. The matched case-control design allowed for a stronger analysis, compared with a non-matched case-control design. This design allowed for removal of the confounding factors of age, gender, and exposure to the medical system. The cases were defined based upon strict, standardized criteria after the initial preliminary case finding using the electronic record. However, the diagnosis of VaD was not based upon pathology diagnosis. The exposures were determined by nurse abstraction and medical record review. There can always be concerns with miscoded information or missing information using medical abstraction. The accuracy of electronic information can depend on the type of information being abstracted from the chart. Nurse abstraction is likely to be more accurate than electronic means alone.[27] In stroke care and evaluation, there appears to be excellent agreement of abstracted information on stroke care using abstractors.[28] Despite all measures to reduce missing information, some missing or misinterpreted information from the medical chart still remained.

The weaknesses of the study included many of the inherent challenges of using a case-control study. The case-control study can provide accurate information in a timely fashion and is frequently used in public health.[29] The case-control study was the most practical study design because VaD is relatively uncommon compared with AD. The inherent challenges of the case-control study included the reporting of the exposures from patients and recording those exposures in the medical chart. Biometric information and demographic information is often recorded in a reproducible manner that does not rely upon self-report. Lifestyle exposures are more difficult because they rely upon self-report. The self-report of alcohol[30,31] and other lifestyle issues like tobacco use affects the exposures in the study, as some subjects may under-report their exposures. Further, information on amount and time of tobacco and alcohol exposure became more sporadic; thus, this information was not reported. The diagnosis of medical conditions was standardized in the study; however, these diagnoses were often made clinically and subject to improper diagnoses or omission. Lastly, we used a simple count method and not a weighted scoring mechanism. This method does not allow for a differential weight for each variable. Despite the limitations, this study provides important insights into the relationship of polyvascular disease and VaD status.

Conclusion

This matched case-control study demonstrates the relationship between increasing incremental vascular risk exposures and VaD status. The total index of all exposures had a positive relationship to VaD status, as did the cerebrovascular index, cardiovascular index, and vascular index. Lifestyle exposures and the lifestyle index did not have a relationship with VaD. Further work will be required to evaluate multiple vascular diseases in different populations and to integrate this potential knowledge within clinical practice.

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Disclosure

The authors report no conflicts of interest in this work.

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