Co-morbidity associated with dementia

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Abstract

Purpose: *The purpose of this study was to identify common co-morbid conditions associated with dementia subtypes and to evaluate the association of hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, and anemia with dementia subtypes relative to controls.*

Methods: *Hospital discharge data were used to identify 15,013 subjects from South Carolina with a diagnosis of dementia between 1998 and 1999. A control group of 15,013 persons without dementia was randomly sampled from hospital discharge records and matched to persons with dementia on the basis of age, race, and gender. Multiple hospitalizations for each patient were merged, and repeated diagnoses during separate hospitalizations were counted once.*

Results: *After adjusting for age, race, and gender, persons with Alzheimer's disease and dementia associated with medical conditions were less likely to be diagnosed with hypertension, diabetes, congestive heart failure, and atrial fibrillation than were controls. Patients with multi-infarct dementia were also less likely to have congestive heart failure, but were more likely to have diabetes. Anemia was not associated with any dementia subtype.*

Conclusions: *There are distinct differences in co-morbid conditions among dementia subtypes. Our research does not support previous studies that suggest a circulatory component to the development of Alzheimer's disease.*

Key words: Alzheimer's disease, cerebral dementia, co-morbidity, dementia, Huntington's chorea, multi-infarct dementia, organic brain disease, Parkinson's disease, senile dementia

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Introduction

Dementia generally occurs in older populations, who are more susceptible to chronic disease. However, patients with dementia are often poor historians with regard to their medical history or symptoms. Knowledge of co-morbid conditions associated with dementia may help alert clinicians to unreported illness and improve prevention and treatment of secondary conditions among these patients. In addition, the study of co-morbid conditions associated with dementia may contribute to the understanding of the etiology of Alzheimer's disease. Proposed biological mechanisms for the development of Alzheimer's disease include increased white matter lesions associated with hypertension,[1,2] dynamic blood glucose changes associated with diabetes,[3] and disturbed blood circulation, resulting from cerebral hypoperfusion

Table 1. Demographic characteristics of persons with dementia subtypes and controls

Characteristic	AD* (n = 11,555)		MID* (n = 1,794)		MED* (n = 1,664)		Controls (n = 15,013)	
	n	%	n	%	n	%	n	%
Age (years)								
40 - 50	16	0.1	17	0.9	180	10.8	215	1.4
51 - 79	4,079	35.3	940	52.4	1,006	60.5	6,023	40.1
≥ 80	7,460	64.6	837	46.7	478	28.7	8,775	58.5
Gender								
Female	8,062	69.8	1,076	60.0	842	50.6	9,977	66.5
Male	3,493	30.2	718	40.0	822	49.4	5,036	33.5
Race								
White	8,481	73.4	1,118	62.3	1,145	68.8	10,567	70.4
Nonwhite	3,074	26.6	676	37.7	519	31.2	4,446	29.6

* AD = Alzheimer's disease; MID = multi-infarct dementia; MED = dementia associated with a medical condition.

and brain infarction.[4] The purpose of this study was twofold: (1) to identify common co-morbid conditions associated with dementia subtypes; and (2) to evaluate the association of hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, and anemia with dementia subtypes to further explore the role of blood circulation in the occurrence of Alzheimer's disease.

Methods

Hospital discharge data were used to ascertain all patients discharged with a diagnosis of dementia from South Carolina hospitals between 1998 and 1999. The ICD-9-CM codes used to identify dementia subtypes were Alzheimer's disease, including senile dementia (290.0-290.3, 290.8-290.9, 331.0), multi-infarct dementia (290.4-290.43), and dementia associated with a medical condition (294.1, 310.1, 331.1-331.9, 332.0-332.1, 333.4). The distribution of medical conditions included in the final category was cerebral degeneration (14.9 percent), Parkinson's disease (9.3 percent), organic brain syndrome (0.4 percent), Huntington's chorea (0.003 percent), and other dementia (75.4 percent). In cases where the dementia subtype differed during repeated hospitalizations, patients with an Alzheimer's disease diagnosis were categorized as such, those with both a multi-infarct dementia diagnosis and a medical condition dementia diagnosis were categorized as "medical condition," and those with multi-infarct dementia across all hospitalizations were categorized as "multi-infarct dementia." After combining multiple hospitalizations into one record, there were 15,013 dementia subjects available for analysis. A control group of 15,013 persons without dementia was randomly sampled from hospital discharge records and matched in frequency to all dementia subtypes combined on the basis of age (five-year age groups), race (white, nonwhite), and gender.

Demographic information was based on the first hospital record, and the total number of diagnoses was summed across records. Repeat diagnoses were counted

Table 2. Number and rank of co-morbid conditions for persons with dementia subtypes and controls

	AD* (n = 11,555)		MID* (n = 1,794)		MED* (n = 1,664)		Controls (n = 15,013)	
	Mean	**SD†**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Number	7.97	3.73	8.13	3.59	7.20	3.40	6.99	4.26
Condition	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**
Fracture of neck of femur	1	8.23	7	2.63	8	1.68	3	3.57
Urinary tract infection	2	8.08	3	8.14	2	4.75	6	4.54
Convulsions	3	3.89	1	9.20	1	5.95	9	1.61
Osteoarthritis	4	3.43	6	2.91	12	1.33	2	4.42
Osteoporosis	5	2.58	8	2.07	13	1.08	5	2.64
Decubitus ulcer	6	2.54	4	3.23	22	0.90	30	0.69
Syncope and collapse	7	2.45	9	1.56	10	1.44	7	1.94
Dysphagia	8	2.19	4	3.23	3	2.82	14	1.27
Congestive heart failure	9	1.79	45	0.39	24	0.84	6	2.34
Essential hypertension	10	1.68	45	0.39	5	2.70	16	1.26

* AD = Alzheimer's disease; MID = multi-infarct dementia; MED = dementia associated with a medical condition.
† SD = standard deviation.

once to prevent overestimation of diagnoses that may have been reported for the same patient during separate hospitalizations. We used four-digit ICD-9-CM codes to calculate the total number of co-morbid conditions and to rank the 10 most common conditions by dementia subtype exclusive of dementia diagnoses for comparison with the control group.

We used unconditional logistic regression to estimate the relative risk of dementia subtypes associated with selected co-morbid conditions while controlling for confounders. The ICD-9-CM codes for these conditions were essential hypertension (401.0-401.9), diabetes mellitus (250.0-250.9), atrial fibrillation (427.3), congestive heart failure (428.0-428.9), and anemia (280.0-281.9). To assess the relation of diabetes and anemia with dementia subtypes, beyond their effect on vascular conditions, we conducted a subgroup analysis restricted to persons without hypertension, atrial fibrillation, congestive heart failure, cardiovascular disease, coronary artery disease, and cerebrovascular disease. Although we matched on the basis of age, race, and gender for all dementia subtypes combined, the distributions differed within dementia subtype. Therefore, analyses are adjusted for these variables to control for their confounding effect on these relationships.

Results

Table 1 presents demographic information for persons with dementia subtypes and controls. Of the 15,013 dementia patients in the study, 11,555 (77.0 percent) had Alzheimer's disease; 1,794 (12.0 percent) had multi-infarct dementia; and 1,664 (11.0 percent) had dementia associated with a medical condition. Patients with Alzheimer's disease were more likely to be 80 or more years old, female, and white as compared to patients with other dementia subtypes and controls.

Table 3. Odds ratios of dementia subtypes associated with selected co-morbid conditions

Condition	Controls (n = 15,103)	AD* (n = 11,555)			MID* (n = 1,764)			MED* (n = 1,664)		
	n	n	OR†	95% CI†	n	OR	95% CI	n	OR	95% CI
Essential hypertension	6,929	4,522	0.74	0.70 - 0.77	805	0.94	0.86 - 1.04	655	0.85	0.76 - 0.95
Diabetes mellitus	3,399	2,385	0.92	0.87 - 0.98	558	1.40	1.26 - 1.56	324	0.79	0.69 - 0.90
Congestive heart failure	3,658	2,311	0.71	0.67 - 0.75	350	0.81	0.72 - 0.92	149	0.44	0.37 - 0.52
Atrial fibrillation	2,851	1,776	0.72	0.68 - 0.77	309	1.02	0.89 - 1.16	172	0.71	0.60 - 0.84
Anemia	1,120	879	0.96	0.88 - 1.06	117	0.88	0.72 - 1.08	87	0.88	0.70 - 1.11

* AD = Alzheimer's disease; MID = multi-infarct dementia; MED = dementia associated with a medical condition.
† Adjusted for age, race, and gender; OR = odds ratio; CI = confidence interval.

Table 2 shows the average number of co-morbid conditions, and the 10 most common conditions for Alzheimer's disease with the corresponding rank of these conditions for persons with other dementia subtypes and controls. The percentages in Table 2 reflect the percentage of all diagnoses identified. Only 69 (0.01 percent) patients had a diagnosis of dementia with no co-morbid conditions. On average, patients with multi-infarct dementia had slightly more co-morbid conditions than did patients with other dementia subtypes or controls. The rank of co-morbid conditions differed by dementia subtype and in comparison with controls. Fracture of the neck of the femur, the most common co-morbid condition among those with Alzheimer's disease, was the third, seventh, and eighth most common co-morbid condition among those without dementia, those with multi-infarct dementia, and those with medical condition dementia, respectively. The most common co-morbid condition associated with multi-infarct dementia and medical condition dementia was convulsions, while the most common co-morbid condition among controls was urinary tract infection. Several co-morbid conditions among those with other dementia subtypes and controls did not appear in the top 10 co-morbid conditions for Alzheimer's disease. For multi-infarct dementia, these were cerebral atherosclerosis (rank 2, 9.09 percent) and chest pain (rank 10, 1.56 percent). For medical condition dementia, these were mechanical complication of a nervous system device (rank 4, 2.82 percent), obstructive hydrocephalus (rank 5, 2.70 percent), urinary incontinence (rank 7, 2.16 percent), and alteration of consciousness (rank 9, 1.62 percent). For controls, these were chest pain (rank 4, 3.20 percent), coronary atherosclerosis (rank 8, 1.62 percent), and retention of urine (rank 10, 1.40 percent).

Table 3 presents the relative risk of dementia subtypes associated with hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, and anemia. After adjusting for age, race, and gender, persons with Alzheimer's disease and medical condition dementia were at reduced risk of hypertension, congestive heart failure, and atrial fibrillation. Along with Alzheimer's disease and dementia associated with a medical condition, there was a decreased risk of congestive heart failure for multi-infarct dementia. Patients with Alzheimer's disease and dementia associated with a medical condition were at decreased risk for diabetes, although it was borderline for Alzheimer's disease while patients with multi-infarct dementia were at increased risk. There was no effect of anemia on any dementia subtype.

After restricting the analysis to persons without vascular conditions (Table 4), there was an elevated risk of diabetes among persons with Alzheimer's disease, and the already elevated risk of diabetes among persons with multi-infarct dementia was more pronounced. Again, anemia appeared to be unrelated to any dementia subtype.

Discussion

Patients with Alzheimer's disease in our study had an average of 7.97 co-morbid conditions, substantially greater than the 2.9 for males and 2.8 for females reported by

Table 4. Odds ratio of dementia subtypes associated with selected co-morbid conditions, restricted to persons without vascular conditions

Condition	Controls (n = 4,200)	AD* (n = 4,128)			MID* (n = 498)			MED* (n = 691)		
	n	n	OR†	95% CI†	n	OR	95% CI	n	OR	95% CI
Diabetes mellitus	563	645	1.24	1.09 - 1.40	131	2.02	1.62 - 2.53	94	1.06	0.83 - 1.36
Anemia	279	317	1.09	0.92 - 1.29	38	1.09	0.76 - 1.56	29	0.77	0.51 - 1.17

* AD = Alzheimer's disease; MID = multi-infarct dementia; MED = dementia associated with a medical condition.
† Adjusted for age, race, and gender; OR = odds ratio; CI = confidence interval.

Wolf-Klein *et al.*[5] Note that their study population was drawn from clients admitted to an outpatient clinic, who were likely to be healthier than the hospitalized patients in our study. The most prevalent co-morbid condition among persons with Alzheimer's disease was fracture of the neck of the femur, while among those with multi-infarct dementia and medical condition dementia, it was convulsions. Among persons without dementia, urinary tract infection was the most common co-morbid condition.

This study examined the association of hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, and anemia with dementia subtypes relative to persons without dementia. The prevalence of these co-morbid conditions differed by subtype. After adjusting for age, race, and gender, persons with Alzheimer's disease and dementia associated with medical conditions were less likely to be diagnosed with hypertension, diabetes, congestive heart failure, and atrial fibrillation than were controls. Patients with multi-infarct dementia were also less likely to have congestive heart failure, but were more likely to have diabetes. Anemia was not associated with any dementia subtype. Although hypertension and atrial fibrillation were not associated with multi-infarct dementia, the elevated risk associated with diabetes is not surprising, since it may result in brain infarcts, the primary cause of multi-infarct dementia.[4] A possible explanation for the lack of association between hypertension and atrial fibrillation and multi-infarct dementia is that persons were more likely to be diagnosed with cerebral atherosclerosis, by definition an underlying cause of multi-infarct dementia.

Research on the association between hypertension and Alzheimer's disease is inconsistent. Some researchers suggest that blood pressure may play a role in the development of Alzheimer's disease, since they are both positively related with white matter lesions.[1,2] In agreement with other researchers, we observed a decreased risk of Alzheimer's disease among persons with hypertension.[6,7] Guo *et al.*[7] speculated that lower blood pressure would lower cerebral blood flow and hasten the decline in mental function. They further suggested that low blood pressure might be a consequence of Alzheimer's disease and its accompanying symptoms of hypoglycemia, weight loss, or deficit in neurotransmitters that regulate blood pressure. The Goteborg study,[8] a 15-year longitudinal study, found that persons who had higher diastolic blood pressure at age 70 were more likely to develop Alzheimer's disease within 10 to 15 years than those with normal blood pressure at age 70 ($p = 0.019$). However, the authors also noted that blood pressure tended to decline with age, and individuals who developed dementia had greater decline in blood pressure than those who did not. This finding may explain the inconsistency in the association of blood pressure and Alzheimer's disease found in cross-sectional studies.

Dynamic changes in blood glucose have also been hypothesized as playing an etiologic role in Alzheimer's disease. We did not see a positive association between diabetes and Alzheimer's disease until we restricted our analysis to patients without vascular conditions. Finch and Cohen[3] reviewed 13 recent studies concerning the association of type II diabetes mellitus and Alzheimer's disease. Five studies showed no significant association, six reported negative associations, and two found positive associations. Due to various limitations of these studies, the authors felt that longitudinal studies were required to establish the relationship between blood glucose and the development of Alzheimer's disease.

Both hypertension and diabetes are risk factors for atherosclerosis and brain infarctions. Results from the Nun study[4] indicate that subjects who met the neuropathologic criteria for Alzheimer's disease and had a history of one or more brain infarctions had significantly lower mean Mini-Mental Status Exam (MMSE) scores than those without a history of brain infarctions ($p < 0.001$). For subjects who did not meet the neuropathologic criteria of Alzheimer's disease, the

mean MMSE scores were similar among persons with and without a history of brain infarctions (p = 0.68). These researchers concluded that brain infarction might play an important role in determining the presence and severity of the clinical symptoms of Alzheimer's disease.

As was the case for hypertension, we saw a reduction in risk of Alzheimer's disease among persons with atrial fibrillation and congestive heart failure. Ott *et al.*[9] reported a strong association between atrial fibrillation and Alzheimer's disease in the Rotterdam study. They suggested that reduced cardiac output associated with atrial fibrillation might lead to inadequate brain perfusion and cause brain damage, resulting in cognitive decline. Atrial fibrillation and congestive heart failure share some common effects on the blood circulation. Both are associated with silent infarctions in the brain,[10-12] which may facilitate the expression of the clinical symptoms of Alzheimer's disease.[4] These hypoxic-ischemic events[13] result in lower cardiac output and hypoperfusion of the brain, which can cause brain damage and subsequent cognitive decline. Ohnishi *et al.*[14] utilized high-resolution single-photon emission computed tomography to demonstrate that regional cerebral blood flow was lower in the bilateral parietal cortices and hippocampus in Alzheimer's disease and multi-infarct dementia patients than in normal controls.

There was no effect of anemia on any dementia subtype in the complete analysis. Beard *et al.*[15] conducted a case-control study and a retrospective cohort study among patients 65 years of age and older at the Mayo clinic. In the case-control study, they found a twofold increase in Alzheimer's disease among persons diagnosed with anemia in the previous year. In the cohort study, 618 persons diagnosed with anemia in 1986 showed no increased risk of Alzheimer's disease. A possible explanation for our finding is that anemia, unlike the other co-morbid conditions, is generally not a condition that requires hospitalization and may be underreported.

Limitations of the present study include the potential for selection bias, diagnostic bias, and misclassification of the co-morbid conditions. The use of hospital discharge data excluded patients with dementia who were not severe enough to be hospitalized. Our results may be biased if the associations of the selected co-morbid conditions with dementia subtypes differed for hospitalized patients and nonhospitalized patients. While imaging techniques have improved diagnostic accuracy, misclassification of dementia is common. Alzheimer's disease, in particular, can only be confirmed on autopsy. In addition, these dementia subtypes are not mutually exclusive within individuals, thus complicating the identification of etiologic pathways. Diabetes may have been underreported if patients' diets were limited prior to hospitalization, thereby lowering normally elevated blood glucose.

Strengths of this study include its population-based nature, its large sample size of patients with dementia subtypes, and a comprehensive group of ICD-9-CM codes to identify hypertension and other selected co-morbid conditions.[16] Our findings suggest that the co-morbid conditions associated with Alzheimer's disease are more similar to those conditions associated with a medical condition than multi-infarct dementia. This does not support previous studies that suggest a circulatory component to the development of Alzheimer's disease. Since the cross-sectional nature of this study does not allow for the correct exposure-outcome temporal sequence, longitudinal studies are necessary to confirm our findings.

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