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High medical co-morbidity and family history of dementia is associated with lower cognitive function in older patients

Lisa A Morrow[a], Beth E Snitz[b], Eric G Rodriquez[c], Kimberly A Huber[b] and Judith A Saxton[b]

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Background. Risk factors for cognitive decline in ageing are multifactorial, including medical co-morbidities and familial genetic risk.

Objectives. To assess the effect of medical co-morbidity and family history of dementia on cognitive performance in older outpatients of family practitioners.

Methods. Analysis of 535 outpatients from 11 practices aged 65 and older, without a diagnosis of dementia. Information on medical co-morbidities, family history of dementia and cognitive test data were obtained.

Results. Patients were classified into high or low medical co-morbidities (<7 versus >8) and positive or negative family history of dementia. After controlling for age, education, gender and depression, global cognitive test scores, as well as memory, executive function, spatial ability and attention were significantly lower for persons having a high number of medical co-morbidities. Cognitive test scores were not significantly different for persons with or without a family history of dementia. A significant interaction between medical co-morbidities and family history of dementia was observed for the global cognitive score, executive function and spatial ability. Those persons with a high number of medical co-morbidities and positive family history of dementia had the lowest performance. Separate regression analysis assessing individual disease risk factors (e.g. hypertension and diabetes) did not find any relationship between specific medical variables and cognitive test scores for any of the subgroups.

Conclusions. A high number of medical co-morbidities in addition to a reported family history of dementia are particularly detrimental to cognitive performance in elderly non-demented family practice patients.

Keywords. Cognitive, family history of dementia, medical co-morbidity, primary care.

Introduction

Advancing age is typically associated with an increasing burden of medical illness. The presence of more than one medical condition—i.e. medical co-morbidity—is common in persons over age 65, with almost half of all Medicare beneficiaries having more than three major medical diseases.[1] Poorer cognitive function is associated with many diseases common in the elderly, with many of the more prevalent diseases, including diabetes,[2] hypertension,[3,4] hyperlipidemia[5] and hypothyroidism,[6] known to be associated with cognitive effects. Conversely, healthy older adults with a few medical problems have been shown to have better cognitive function.[7]

Few studies, however, have examined the impact on cognitive function of co-morbid illnesses. The Framingham study found a strong relationship between medical co-morbidity and cognitive function, though utilizing only a very limited measure of cognitive status—the Mini-Mental State Exam (MMSE).[8] A later study looked at medical history—as defined by

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[a]Department of Psychiatry, [b]Department of Neurology and [c]Department of Geriatric Medicine, University of Pittsburgh, Pittsburgh, PA, USA. Correspondence to Lisa A Morrow, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA; E-mail: morrowla@upmc.edu

past and present symptoms, physical limitations and medication—in relation to performance on verbal and non-verbal cognitive tests and found greater medical problems associated with poorer performance on tests of non-verbal ability.[9] A study of elderly patients in an inpatient rehabilitation setting also found illness burden related to cognitive deficits, with executive-type tasks (measures of reasoning and judgement) being most sensitive to cumulative medical illness.[10]

Another risk factor for poor cognitive function in the elderly is a family history of dementia. A positive family history has been associated with a higher age-specific risk for dementia as well as poorer cognitive outcome in studies of elderly adults,[11–14] though family history has not always emerged as a significant risk factor.[15,16] Studies addressing specific cognitive test scores have found that first-degree biological relatives of patients with diagnosed Alzheimer's disease (AD) have poorer memory scores compared to controls[17] and differences in the pattern of recall on memory tests.[18]

Given that both medical co-morbidity and family history of dementia are risk factors for poor cognitive performance, a logical question is whether having both risk factors increases the risk for poor cognition. To that end, the present study examined medical co-morbidity and family history of dementia in a large cohort of community-dwelling adults aged 65 and over from 11 primary care practices. Measures included a multidomain neuropsychological battery, assessment of current depressive symptoms, detailed medical chart review and queries for family history of dementia. We hypothesized that the presence of a high burden of medical illness in addition to a family history of dementia would be particularly detrimental to cognitive test performance in this elderly non-demented sample.

Methods

Study sample

Participants in this study were enrolled as part of a parent study examining the effect on patient care of providing cognitive test reports of older adults to family physicians. Data were entered for all 535 patients consented into the parent study from 11 family practices in the greater Pittsburgh area. Practices were located in urban (n = 2), rural (n = 2) and suburban settings (n = 7). Patients were eligible for recruitment if they (i) were aged 65 and over and (ii) did not have a diagnosis of dementia. Patients were first approached by their physicians who were asked to refer all patients in their practice over the age of 65. Physicians were instructed not to refer only those patients they thought might have some cognitive problems. No subjects who were acutely ill were tested. After a telephone screening and initial consent and interview, potential participants were excluded if they had significant sensory deficits, which would preclude cognitive testing or an MMSE[19] score of $\leqslant$18 indicating significant cognitive impairment consistent with dementia.

Within the 11 practices, 91 patients were referred to the study but elected not to participate. Comparisons between those who did and did not participate demonstrated no significant differences regarding originating study physician, office location or assignment of the physician office to either intervention (receive a cognitive report) or treatment as usual (no cognitive report sent to physician). The study was approved by the University of Pittsburgh Institutional Review Board and was conducted in accordance with the Helsinki Declaration with all participants providing written informed consent.

Neuropsychological assessment

A comprehensive neuropsychological battery was administered to all participants. The battery consisted of 19 standard cognitive tests designed to detect mild cognitive deficits and pre-dementia cognitive changes. 'Memory' tests included the Consortium to Establish a Registry for Alzheimer's Disease Word List Learning Test[20] with delayed recall, Wechsler Memory Scale-Revised Logical Memory I and II[21] and the modified Rey–Osterrieth figure with immediate and delayed recall.[22] Tests of 'executive function' included Wechsler Adult Intelligence Scale-Revised (WAIS-R) Backward Digit Span,[23] controlled oral word association test, Part B of the Trail Making Test,[24] the WAIS-R Digit Symbol[23] and Clock Drawing. 'Spatial ability' included the modified Rey–Osterrieth Copy and the modified WAIS-R Block Design. Tests of 'attention/psychomotor speed' included WAIS-R Digit Span forward and Part A of the Trail Making Test[24]. Tests of 'language abilities' included the Boston Naming Test[25] and semantic fluency (animals).[26]

Clinical information and medical record review

Demographic information included age, education, gender and marital status. In addition, participants were queried as to whether there was a positive family history of dementia or AD (35 of the 535 participants were not queried regarding family history of dementia due to adding this question shortly after the start of the study). Participants also completed a modified version of the Center for Epidemiological Studies-Depression (CES-D) scale.[27] Each participant's medical records from their physician's offices were reviewed and extracted information (conducted by a registered nurse practitioner using a structured chart abstraction procedure[28]) included a complete medical problem list over the previous 2 years.

Statistical analyses

Cognitive test scores were converted to z-scores and a mean z-score for each cognitive domain was

determined (memory, executive, spatial, attention and language), as well as a global cognitive *z*-score (mean of the five domains). Persons were categorized into low or high number of medical problems, based on a cut-point of 8, which was the 50th percentile for the overall group (range 1–30). Family history of dementia was either negative (no history) or positive (self-report or medical chart note of a family member with dementia or AD). Associations between cognitive performance and medical co-morbidities (high versus low) and family history of dementia (no versus yes) were tested via two-way analysis of covariance (ANCOVA) for each of the five cognitive domains and the global cognitive score (dependent variable), with inclusion of age, education, gender and depression score as covariates. To evaluate whether specific individual medical diseases (e.g. diabetes, hypertension, etc.) were associated with cognitive performance for the four subgroups, regression analyses were done with age, education, gender and depression entered on the first step and medical disease variables entered stepwise on the second step.

Results

Demographic and clinical characteristics of the total participant sample are presented in Table 1. Of note, the mean MMSE score was high (28.2) as expected due to exclusion of potential participants with chart diagnoses of dementia and instructions to physicians to refer any patient over age 65, not just those who they believed had cognitive deficits. There was, however, a clinically significant range of scores on the MMSE (21–30). The mean depression score was also very low but with a clinically significant range present (0–17). The average number of medical problems was 8.1 with an average of 7.9 prescription medications. The most frequent medical problems noted were hypercholesterolemia (72.7%), hypertension (69.5%) and arthritis (62.6%). Smaller percentages of other medical disorders were noted: gastroesophageal reflux disease (28.8%), type II diabetes (26.5%), coronary artery disease (24.7%), chronic obstructive pulmonary disease (COPD, 11.6%) and stroke (4.9%). Other diseases accounted for <3% of the sample (e.g. sleep apnea and chronic pain).

TABLE 1 *Demographic and clinical characteristics of participants (total n = 535)*

	Mean or *n*	SD or %	Range
Age	73.1	6.0	65–93
Education (years)	13.89	2.9	6–25
Females	315	58.0%	–
MMSE score	28.1	1.8	21–30
Modified CES-D score (0–20 points)[a]	2.1	2.8	0–17
Number of prescription medications	7.9	4.1	0–27
Number of medical problems coded in chart	8.1	3.8	0–30
Medical chart note of			
Hypertension	372	69.5%	–
Hypercholesterolemia	389	72.7%	–
Arthritis	335	62.6%	–
Gastroesophageal reflux disease	154	28.8%	–
Diabetes mellitus II	142	26.5%	–
Coronary artery disease	132	24.7%	–
Thyroid	115	21.5%	–
COPD	62	11.6%	–
Stroke	26	4.9%	–

[a]Higher scores indicate more depressive symptoms.

Within the subgroups, there were no differences on education or marital status, but differences were noted for both gender and age. That is, the group with high medical problems and negative family history was older and made up of relatively more men than the other three groups. Numbers of prescriptions were, not surprisingly, significantly higher for those in the high medical problem groups. Significant differences were also noted for depressive symptoms, with higher CES-D scores noted in persons with more medical problems.

A two-way ANCOVA was computed for each of the five cognitive domain scores as well as the global cognitive *z*-score as the dependent variables. Age, education, gender and depression scores were entered as covariates and medical problem and family history as independent variables. There was a significant main effect for medical problems for the global cognitive test score as well as four of the five cognitive domains [all *P*-values < 0.01, with exception of language ($P = 0.13$)]: persons with more medical problems had significantly lower test scores in most cognitive domains. There was no main effect for family history of dementia for any of the individual cognitive domains or the global cognitive score (all *P*-values > 0.10). A significant interaction between medical problems and family history of dementia was obtained for the global cognitive score [$F(1,492) = 5.75$; $P < 0.02$] and scores for both the executive [$F(1,494) = 4.73$; $P < 0.03$] and spatial domains [$F(1,498) = 4.52$; $P < 0.03$]. The attention domain just missed the acceptable level of significance [$F(1,492) = 3.45$; $P < 0.06$]. The interaction indicates that the presence of both a high number of medical problems and a family history of dementia was associated with significantly poorer global test performance, as well as poorer performance in two of the five specific domains—executive and spatial function. This trend was apparent for all the cognitive domains but reached significance for only the executive and spatial domains.

To determine if certain medical problems were related to poorer cognitive performance, regression analyses were run for the four separate groups

(low medical problems negative family history, low medical problems positive family history, high medical problems negative family history and high medical problems positive family history) predicting overall cognitive performance. Age, education, gender and depression were entered on Step 1 as covariates and nine of the most frequent medical disorders (hypertension, hypercholesterolemia, arthritis, gastroesophageal disease, diabetes, coronary artery disease, thyroid disease, COPD and stroke) entered stepwise on Step 2. There were no significant relationships between any of the medical disorders and global cognitive test score. Individual cognitive domains (e.g. memory, executive, etc.) were also examined in separate regressions and none of the medical disorders were related to test performance in any of the single domains.

Summary and discussion

The goal of the present study was to assess cognitive performance in a large group of healthy elderly outpatients in relation to medical co-morbidities and family history of dementia. Overall, we found that a high number of medical problems were significantly associated with poorer cognitive test performance. Although the presence of a family history of dementia was not, in itself, associated with lower cognitive test scores, having both a family history of dementia and a high number of medical problems was particularly detrimental to cognitive status, even after controlling for age, education, gender and number of depressive symptoms. This finding was noted for the global cognitive score as well as for single domains of executive function and spatial function. While not significant for the other three domains, attention, memory and language, the scores were all in the same direction. That is, those persons who had both a family history of dementia and a high number of medical co-morbidities had the lowest test scores compared to persons who were not positive for either conditions.

The above results suggest that a combination of risk factors (both a family history of dementia and high disease burden) may impart greater risk for cognitive impairment than either risk factor alone. While some studies have found that family history is associated with an earlier age of onset of dementia or poorer cognitive test scores,[12,17] other studies have not demonstrated a link between cognitive function and a positive family history.[16,18,29] The latter studies are consistent with our current findings. On the other hand, it is fairly well established that higher disease burden places one at greater risk for poorer cognitive functioning.[10,30] Our results show that the additional component of positive family history seems to compromise cognitive function above and beyond either individual risk factors. Studies looking at cognitive function in the elderly typically address only single-risk factors with less attention to multimorbidity issues. Our results demonstrate the importance of a comprehensive assessment of multiple co-morbid medical disorders and the association of total burden illness with cognitive function.

It is of interest to consider the possible mechanism, which may account for these findings. Does family history increase vulnerability to the effect of cumulative medical illness or does illness burden lower a threshold for the manifestation of the familial risk? No specific disease such as hypertension or diabetes or cardiovascular disease predicted poor cognitive test scores—and this was true for all groups, even those with both high medical problems and positive family history. At this point, therefore, we cannot point to particular medical disorders associated with greater risk for lower cognitive performance in the presence of a positive family history. While prior studies suggest that vascular disorders are prominent risk factors for mild cognitive impairment and development of AD, we did not find a relationship between diseases in this class (e.g. diabetes, hyperlipidemia and stroke) and cognitive test performance.[31] We also gave equal weight in the analysis to the different diagnoses and co-morbidity was assessed in a binary fashion (>7 versus <7). It may be that for this type of cohort—independent, community-dwelling non-demented elderly—risk derives from the magnitude of burden of illness. That is, a high load of medical problems is additive and no one single disease is more detrimental than another.

While we noted that test scores for those persons positive for family history and high medical co-morbidity were lower across all test domains, only executive function and spatial function were significant single domains (the overall global score was also significant). These two areas of cognitive function have implications for several important daily activities confronting the elderly—medication adherence and driving. There is increasing evidence that the specific cognitive skills most critical to one's ability to understand and comply with complex medication regimens involve 'executive functions'.[32] This broad conceptual group of cognitive processes includes mental flexibility, complex action planning, ability to inhibit responses to distracting stimuli and abstract reasoning. Thus, compromises in executive function may be particularly harmful to medication adherence. Poorer spatial skills, along with executive skills, may have implications for driving, as poor visuospatial performance and planning skills have been found to be predictive of risky driving.[33]

Limitations to the study include the fact that family history was based on only self-report and/or medical chart review—we do not know if these individuals carry a genetic risk for dementia (e.g. Apolipoprotein E). In addition, persons in this study constitute

a limited group of elderly attending family physician offices and are primarily Caucasian, female and have, on average, education beyond high school. Our findings suggest that a potential interaction between familial history of dementia and a high number of diagnosed diseases increases the likelihood of cognitive impairment in ageing adults. While a positive genetic history for dementia is not amenable to alteration, improving health status, even in later life, is feasible. Our findings suggest that efforts to lower cumulative medical burden in the elderly may benefit cognitive function, particularly in persons with a family history of dementia.

Declaration

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