Hypertension Increases the Probability of Alzheimer's Disease and of Mild Cognitive Impairment in an Arab Community in Northern Israel

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Key Words

Dementia · Alzheimer's disease · Mild cognitive impairment · Hypertension

Abstract

Background: We aimed to determine whether vascular risk factors are associated with Alzheimer's disease (AD) and mild cognitive impairment (MCI) in an elderly Arab population.

Methods: An Arabic-speaking team performed a door-to-door survey of consecutive residents aged ≥ 65 years. We estimated the odds of AD or MCI versus normal controls as a function of age, gender, education and presence of vascular factors by multinomial logistic regression with interactions.

Results: Out of 767 subjects (54% men), 444 were cognitively normal, 234 had MCI and 89 had AD. AD was significantly associated with hypertension ($p = 0.01$; OR = 2.08; 95% CI: 1.18–3.65), age ($p < 0.0001$; OR = 1.19; 95% CI: 1.14–1.24), female gender ($p = 0.0016$; OR = 3.06; 95% CI: 1.53–6.15) and education ($p = 0.0002$; OR = 0.75; 95% CI: 0.65–0.88). MCI was significantly associated with hypertension ($p = 0.0042$; OR = 1.69; 95% CI: 1.25–2.44), age ($p < 0.0001$; OR = 1.06; 95% CI:

1.03–1.09) and education ($p < 0.0001$; OR = 0.76; 95% CI: 0.71–0.83), but not with gender. **Conclusions:** Hypertension, older age and low education significantly increase the probability of AD and MCI. The effect of hypertension on the odds of AD versus controls is over and above the effects of age, gender and education. For MCI versus controls there is no gender effect, and the effect of hypertension is over and above the effects of age and education. Copyright © 2009 S. Karger AG, Basel

Introduction

Alzheimer's disease (AD) has been shown to be associated with age, female sex, vascular risk factors (e.g., hypertension, diabetes and dyslipidemia) [1], ethnicity, low education, alcohol consumption and APOE status. In this report, we examined the relationships of age, sex, education and vascular risk factors with the risk of mild cognitive impairment (MCI) and AD in an elderly population remarkable for a high prevalence of dementia, low levels of schooling, high consanguinity

rates (a consanguinity rate of 52.9% was reported in a similar population in the center of the country in the 1960's) [2] and low rates of intervillage marriage. Moreover, the population was homogenous with respect to ethnicity (Arabic) and religion (Muslim), minimal alcohol consumption [3], obesity (3 out of 4 women by the age of 60 years) [4], rural environment and low socioeconomic status.

A previous study of this population found old age, female gender and lack of education to be risk factors for the development of AD [5]. Given the high rates of consanguinity and the increased prevalence of autosomal recessive diseases, several genetic studies have been performed in this population [5–7]. Considering the high consanguinity rates, genetic (mutations or susceptibility polymorphisms) and epigenetic factors may contribute to the relatively high rates of dementia. Although the *APOE4* allele is rare in this population, an association between polymorphisms in the angiotensin-converting enzyme gene and AD has been reported [6]. This finding adds further support to the growing evidence linking vascular risk factors to cognitive decline. The contribution of vascular risk factors to the occurrence of cognitive decline on the background of low education remains to be elucidated.

Methods

Study Design

The study is a door-to-door observational study of the elderly population of Wadi Ara villages in northern Israel.

The study was approved by the Institutional Ethics Committee of the Sheba Medical Center according to guidelines from the Israeli Ministry of Health, and was also reviewed by the Institutional Review Boards of the University Hospitals of Cleveland, the Case Western Reserve University, Boston University and the University of Louisville. All participants signed a written consent form in Arabic. In the event of the subject being illiterate, the interviewer read the consent form to the subject, who then signed by fingerprinting with the index finger of his/her dominant hand.

Study Population

Wadi Ara (the Ara Valley) is located in northern Israel and has a population of 81,400 Arab inhabitants, of whom 51% are men. The elderly cohort aged ≥ 65 years included 2,067 residents (2.5%) on prevalence day (January 1st, 2003), according to the Israel Central Statistics Bureau.

Eligibility Criteria

All Wadi Ara residents aged ≥ 65 years on prevalence day (January 1, 2003) were eligible. There were no selection criteria.

Sources and Methods of Participant Ascertainment

The research team visited consecutive houses in Wadi Ara villages and approached all eligible subjects living in these houses. We herein report the results concerning the first 935 elderly subjects approached between January 2003 and December 2007.

Subject Evaluation

This work is part of an epidemiological study of aging-related brain disorders in Wadi Ara [8–10]. The research team including a neurologist (M.M.) and an academic nurse (A.A.), both fluent Arabic speakers, examined all subjects in their own homes. They all resided either with their spouse or in the home of a close relative. None lived alone and none of the subjects were institutionalized, as is the norm in this population. Information about medical and family history, medication use, daily activities (social, personal, occupational and recreational), behavior, cognitive abilities and changes in the above was obtained by a nurse-led structured interview of the subject and a close relative. During the second visit, the neurologist performed a complete neurological examination including the motor part of the Unified Parkinson's Disease Scale on all subjects.

Cognitive Instruments

Arabic translations of the Mini-Mental State Examination (MMSE; maximum score = 30) and the Brookdale Cognitive Screening Test (BCST; maximum score = 24) were used. The BCST was developed at the Brookdale Institute of Gerontology, Jerusalem, Israel, for use in populations with high illiteracy rates [11]. It includes items on orientation, language, memory, attention, naming, abstraction, concept formation, attention, praxis, calculation, right-left orientation and visuospatial orientation. The Arabic versions of the MMSE and the BCST have been validated, and norms have been published [10]. Since the MMSE involves several tasks that are dependent on literacy, these items scored 0 in subjects with no formal education. A highly significant correlation between MMSE and BCST scores in normal subjects has previously been reported by our group ($r = 0.852$; $p < 0.0001$). This correlation was of the same magnitude for men ($r = 0.8223$) and women ($r = 0.854$; $p < 0.0001$ for both) [10].

Cognitive Classification

All subjects were classified as healthy (cognitively normal), AD, MCI, vascular dementia, Parkinson's disease (PD) dementia, other dementia or not classifiable according to accepted criteria [12–15]. Since MMSE and BCST scores are strongly dependent on education in both genders in this population, we did not use cut-off scores for cognitive classification [10].

Cognitively Normal

A subject was defined as cognitively normal if there were no complaints about memory impairment or any other cognitive domain, no evidence of such disturbance according to the informant history or neurological examination, and no evidence of impairment in the activities of daily living due to cognitive disturbances [10].

Mild Cognitive Impairment

Subjects were classified as MCI if they had an impairment of cognitive function on examination, with a Clinical Dementia Rating Scale score of 0.5 [16] and an informant record of cogni-

tive decline, but did not have functional impairment in their activities of daily living that would qualify for dementia when assessed by the informant interview and/or physical examination [17, 18].

Alzheimer's Disease

Dementia was diagnosed according to the DSM-IV criteria and those of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and AD by the NINCDS-ADRDA criteria for probable or possible AD [12, 19].

Vascular Dementia

Vascular dementia (VaD) was diagnosed according to the ICD-10 criteria. Thus, a history consistent with cerebrovascular disease, pyramidal signs and previous cerebral imaging were actively sought to substantiate a diagnosis of VaD.

'Not Classifiable'

The category 'not classifiable' included subjects with complex medical conditions or advanced systemic disease in whom it could not be determined whether the cognitive impairment was due to the underlying medical condition or the neurodegenerative disease.

Three neurologists (M.M., R.S. and R.I.) reviewed the results of the field examination of each subject in a bimonthly conference and formed a consensus diagnosis.

Vascular Risk Factors

All subjects had medical insurance as required by law in Israel (the National Health Insurance Law, 1995) and regularly attended their family physician's medical practice. The presence of hypertension, hyperlipidemia, diabetes and cardiac disease was determined by the history, informant history and review of relevant documentation such as medical reports and drug prescriptions. When prescriptions of medications used to lower blood pressure, lipids or antidiabetics were present, the informants were asked accordingly about the presence of the relevant risk factors.

Blood pressure was measured on each visit. Hypertension was defined according to the criteria for hypertension of the 7th Report of the Joint National Committee (i.e., systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg) [20].

Statistical Analysis

Statistical analyses were performed using SAS (Statistical Analysis Software). Multinomial logistic regression was used to estimate the odds of AD or MCI versus normal controls as a function of age, gender, education and vascular risk factors (hypertension, diabetes, hyperlipidemia and cardiac disease) defined as dichotomous outcomes. Education was measured by the number of years of school attendance (school years) and was treated as a continuous variable. The model also included gender, age, education, the 4 vascular risk factors (as described above) and the interaction of gender with age, education and each of the 4 vascular risk factors as well as 2 more interactions: age-gender and gender-education. Thus, altogether, the model consisted of 13 explanatory variables. In the case of missing information on any of the explanatory variables, the subject was deleted from the analysis.

Fig. 1. Study population.

Results

Of the 935 eligible subjects approached (fig. 1), 902 agreed to participate in the study (3.5% refusal rate). Eighteen were excluded for the following reasons: recent head trauma ($n = 2$), recent ischemic stroke ($n = 3$), end-stage renal failure ($n = 2$), metastatic carcinoma ($n = 2$), systemic disease ($n = 7$) and severe depression ($n = 2$).

In total, 884 subjects were included in the study. Among these, 86 had other diagnoses, including VaD ($n = 39$) and PD ($n = 13$), or were 'not classifiable' ($n = 34$) (fig. 1).

Thus, the final cohort that was included numbered 767 subjects of whom: (a) 444 subjects were diagnosed as cognitively normal (mean age $\pm$ SD: 71 ± 6 years; 40% females); (b) 234 were diagnosed with MCI (mean age: 73 ± 6 years; 61% females), and (c) 89 were diagnosed with AD (mean age: 78 ± 8 years; 74% females). Of these 767 subjects, 38 who had missing data on at least 1 of the variables were excluded from the regression analysis.

The frequency of risk factors in each cognitive group is shown in table 1.

Table 1. Demographics and vascular risk factors in the study population

	Normal	MCI	AD	Total
Number	444	233	77	754
Mean age $\pm$ SD years	71 $\pm$ 6	73 $\pm$ 6	78 $\pm$ 8	73 $\pm$ 6
Males	268 (60)	91 (39)	20 (26)	379 (50)
Zero school years				
Male	35 (13)	30 (35)	7 (30)	72 (19)
Female	97 (56)	110 (79)	45 (68)	252 (65)
Hypertensive	213 (48)	142 (61)	54 (70)	409 (54)
Diabetic	145 (33)	100 (43)	35 (45)	280 (37)
Hyperlipidemic	147 (33)	70 (30)	21 (27)	238 (32)
Cardiac disease	128 (29)	79 (34)	29 (38)	236 (31)

Values are numbers with percentages in parentheses, unless otherwise indicated.

Table 2. Multinomial logistic regression analysis of vascular risk factors

	OR	95% CI	p
AD vs. controls			
Hypertension	2.08	1.18–3.65	0.01
Age	1.19	1.14–1.24	<0.0001
Female gender	3.06	1.53–6.15	0.0016
Education	0.75	0.65–0.88	0.0002
MCI vs. controls			
Hypertension	1.69	1.25–2.44	0.0042
Age	1.06	1.03–1.09	<0.0001
Education	0.76	0.71–0.83	<0.0001

All interactions were statistically nonsignificant.

Women had less years of schooling. Only 35% of women, versus 81% of men, had any school education. Multinomial logistic regression analysis showed that AD was significantly associated with hypertension ($p = 0.01$; OR = 2.08; 95% CI: 1.18–3.65), age ($p < 0.0001$; OR = 1.19; 95% CI: 1.14–1.24), female gender ($p = 0.0016$; OR = 3.06; 95% CI: 1.53–6.15) and education ($p = 0.0002$; OR = 0.75; 95% CI: 0.65–0.88). No other variables were chosen (table 2).

MCI was significantly associated with hypertension ($p = 0.0042$; OR = 1.69; 95% CI: 1.25–2.44), age ($p < 0.0001$; OR = 1.06; 95% CI: 1.03–1.09) and education ($p <$

0.0001; OR = 0.76; 95% CI: 0.71–0.83) but not with gender (table 2).

We note that the multinomial logistic regressions included interaction terms which were found statistically nonsignificant.

Discussion

In this elderly population with low levels of education and a high prevalence of dementia, we found hypertension to be an independent risk factor for AD and MCI, in addition to older age and poor education.

Numerous studies have examined the relationship between hypertension and cognitive function. The relationship between blood pressure and dementia risk is not yet entirely clear. Many longitudinal studies have found that the risk of dementia and cognitive impairment is associated with high blood pressure [21, 22], but others have found that low blood pressure is associated with dementia [23] or that there is no association [24–26]. Possible explanations for these discrepancies include that the relationship between hypertension and dementia is not monotonic and is age-specific, or that there may be a delay from exposure to clinical manifestation. Recently, however, it has been shown that even amongst the ‘oldest old’ (≥ 80 years) there may be a benefit in terms of cognition from lowering blood pressure [27]. In the present study, we could not examine the effect of treatment since we did not know whether the subjects were compliant and whether the treatment was effective.

A prospective longitudinal study of 9,704 women found that hypertension was strongly associated with cognitive decline in the setting of an incident stroke and only weakly associated in women who were stroke-free (OR = 4.07; 95% CI: 1.37–12.1, and OR = 1.13; 95% CI: 1.04–1.22, respectively) [28].

An analysis of data from the Rotterdam study showed that a high diastolic pressure 5 years before MRI in patients with untreated hypertension was associated with hippocampal atrophy, whereas a low diastolic pressure at the time of MRI in patients with treated hypertension was associated with amygdala and hippocampal atrophy [29]. These findings suggest that vascular disease may contribute to the atrophy of structures linked with Alzheimer pathology.

While most studies of blood pressure and cognition have examined the middle-aged or elderly, the impact of hypertension in low schooling populations such as the present one has not been extensively investigated. In this

study, hypertension, older age, female gender and low education were all risk factors for dementia. It is possible that there is a greater susceptibility to the deleterious cognitive effects of hypertension amongst women. The literature on these issues, however, is inconsistent. The Women's Health Initiative Memory Study, a large prospective study, did not demonstrate an independent association of hypertension and high blood pressure at baseline with MCI or probable dementia over time in older, cognitively intact, postmenopausal women [25]. However, on a genetic level, Crawford et al. [30] reported possible gender-specific interactions with respect to the angiotensin-converting enzyme gene. Artero et al. [31] reported a gender-specific risk profile for the progression of MCI to dementia, with men being more susceptible to the effects of stroke and women to depression. Azad et al. [32] showed that women may be more susceptible to develop dementia in the presence of diabetes and midlife obesity.

A unique feature of our population is the marked gender disparity in levels of formal education. Consistent with the cognitive reserve hypothesis, education has been reported to be a protective factor for cognitive decline [33–35]. Most of these studies focused on higher education and few studies exist on populations with high illiteracy rates [36]. In the current study, only 44% of the women among the cognitively healthy and 87% of the men had any formal education, and among persons with MCI or AD, 26% of the women and 68% of the men had any education, yet education still had a protective effect on cognitive decline.

The high prevalence of cognitive impairment observed in the present cohort has been reported in an earlier study [5]. Our study also found a high prevalence of MCI. This may be a result of low education, but the link to hypertension or additional risk factors has not yet been defined.

We did not use MMSE cutoffs to define MCI because of the low rates of literacy and, thus, low MMSE scores. However, in order to determine how using an MMSE-based definition of MCI would influence prevalence of MCI in this cohort, we 'reclassified' each subject, using the mean -1 (SD) MMSE score (based on previously published norms for this population) [10] to define the lower limit of normal for each gender and schooling groups (0–4, 5–8 and >8 years) as reported for this population at the relevant age group [10]. While the present study classified 444 subjects as normal and 234 as MCI, the method of MMSE cutoffs classified 411 as normal and 267 as MCI. Thus, the proportion of MCI patients would be even higher when using an MMSE-based definition of MCI.

Notably, 208 of the 234 patients classified in this study as MCI would be classified as MCI by MMSE cutoffs, and 385 of the 444 normal subjects would be classified as normal. The discrepancies in classification mainly occurred in women: 59 subjects (25 men, 34 women) originally classified as normal would be classified as MCI, and 27 subjects originally classified as MCI would be classified as normal (5 men, 22 women).

This population is known to have high rates of cardiovascular risk factors [37]; however, we did not find any relationship between MCI/AD and cardiovascular risk factors other than hypertension. This may be partly explained by the study methodology. Some statistical power may have been lost by dichotomizing the variables of cardiovascular risk rather than subdividing the categories according to severity or treating them as continuous variables, but the large sample size compensated for this, as evidenced by very low p values. The use of logistic regression may be based on an incorrect assumption that putative risk factors act in an independent rather than synergistic manner [1]. Also, a survival bias may attenuate the risk associated with cardiovascular factors. In cross-sectional studies, one may observe both the effect of the risk factors on developing cognitive decline and the effect of the same parameters on subjects' survival after neurodegenerative processes have already been established.

Another caveat against our results is the sensitivity of the cognitive instruments employed in our door-to-door study design. More extensive cognitive testing would be necessary to diminish potential misclassification. On the other hand, this door-to-door study probably had minimal selection bias. The refusal rate was low (3.5%). There were no selection steps prior to subject evaluation. However, the nature, degree and direction of the effect of exposure to a risk factor may change over time and can only be assessed prospectively.

Of note, in contrast to AD, female gender was not a risk factor for MCI. MCI, rather than being one entity, is likely to be the phenotypic expression of several possible pathologies or combinations of pathologies, or simply due to normal aging. Indeed, it may be more correct to consider neurodegeneration as a disease spectrum and to define cognitive outcome as a continuous variable [38] rather than arbitrarily categorizing into 'normal', 'MCI' and 'dementia'.

Intrinsic to the issue of determining the contribution of vascular risk factors to the risk of AD is the issue of distinguishing AD and VaD. Cerebral imaging is of use in this respect; however, there is no consensus on the sig-

nificance of mild ischemic changes nor on the criteria for its diagnosis [39–41]. On a pathological and clinical level, more than one neurodegenerative pathology may be present and have a synergistic effect. Indeed, in current thinking most patients can be viewed as existing somewhere along the spectrum between pure AD and pure VaD [42, 43]. Although the participation rate was very high (96.5%), there was a high refusal rate for cerebral imaging, thus routine imaging was not possible. However, patients with a previous stroke on the basis of clinical features, or with VaD according to ICD-10 criteria, were excluded.

Concerning the treatment of hypertension, although there have been conflicting data in the past, there is now increasing evidence that improved blood pressure control might reduce dementia incidence [44–46]. This inverse relationship between blood pressure and cognition may extend to the ‘normotensive’ range, as suggested by data from a recent cross-sectional observational study [47] and to the very elderly [45].

With respect to putative pathogenetic mechanisms linking vascular risk factors and dementia, it is not clear whether atherosclerosis and neurodegeneration are independent and convergent mechanisms, or whether atherosclerosis directly contributes to neurodegeneration. Our data show that age, female sex, low education and hypertension are all risk factors for AD. These results may be extrapolated to other populations with high rates of illiteracy where women are at the highest risk of MCI and AD.

Acknowledgments

The authors were supported in part by the NIH (R01 AG017173, R01 AG09029, R01 HG/AG02213), the Joseph and Florence Mandel Research Fund, the Nickman Family, GOJO Corp., the Fullerton Foundation and the Institute for the Study of Aging.

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