Antihypertensive Therapy Is Associated with Reduced Rate of Conversion to Alzheimer's Disease in Midregional Proatrial Natriuretic Peptide Stratified Subjects with Mild Cognitive Impairment

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Background: Hypertension is a major risk factor of Alzheimer's disease (AD); however, controlled studies on the effect of antihypertensive treatment on the risk of dementia are inconclusive. Therefore, a biological marker that predicts individual response to antihypertensive treatment would be of high clinical relevance. Midregional proatrial natriuretic peptide (MR-proANP), an inactive surrogate molecule of the mature atrial natriuretic peptide, is related to circulatory function and hypertension.

Methods: A sample population of 134 subjects with mild cognitive impairment (MCI) was followed for up to 6 years. Multivariable Cox regression analysis was conducted to predict conversion to AD based on all relevant variables.

Results: Baseline MR-proANP was significantly increased in the AD converter group ($p < .0001$). The conversion rate of patients treated with antihypertensive drugs was significantly reduced only in patients with elevated MR-proANP at baseline ($p = .046$). Using an optimized MR-proANP cutoff of 74 pmol/L, representing a value in the upper normal range, treatment with antihypertensive drugs reduced the conversion rate to AD by 36% ($p = .035$) for patients with levels >74 pmol/L. Further subgrouping by age (>/≤ 72 years at baseline) increased the positive correlation of antihypertensive treatment and MCI outcome for patients below the age of 72 years (conversion rate reduced by 74%, $p = .016$).

Conclusions: These data seem to support the notion of a potential impact of circulatory function for the prognosis of AD at a prodromal stage. The MR-proANP levels may be useful to predict the effect of antihypertensive treatment on conversion rates to AD in subjects with MCI.

Key Words: Alzheimer's disease, antihypertensive therapy, antihypertensive treatment, microcirculatory function, mild cognitive impairment, MR-proANP

There is growing evidence that vascular risk factors contribute to the pathogenesis of Alzheimer's disease (AD) (1,2). Various vascular risk factors are associated with an increased risk of dementia and AD, including systolic and diastolic hypertension, hypercholesterolemia, diabetes mellitus, obesity, lack of exercise, and smoking (3–5). In epidemiological studies, treatment with antihypertensives, statins, or nonsteroidal anti-inflammatory drugs and regular physical exercise are associated with a decreased risk of dementia and AD (5–8).

Mild cognitive impairment (MCI) is a syndrome defined as cognitive decline that is greater than expected for an individual's age and level of education but does not interfere notably with activities of daily life (9). Most subjects with MCI will progress to AD at a rate of 10% to 15% per year compared with healthy subjects of comparable age who convert at a rate of 1% to 2% per year (10,11). Mild cognitive impairment can thus be regarded as a risk state for dementia, and its identification potentially enables secondary prevention by controlling risk factors such as systolic hypertension. Vascular risk factors increase the rate of progression from MCI not only to vascular types of dementia (12) but also to AD (13) and accelerate the rate of cognitive decline in clinically manifest AD (14). Postmortem histopathological studies further support the link between cerebrovascular pathology, vascular risk factors, and AD. Brains of subjects with AD show vascular pathology in up to 90% of cases, including cerebral amyloid angiopathy, cerebral infarction and microinfarction, white matter lesions related to small vessel disease, and microvascular hemorrhages (15–17). In autopsy studies, there is evidence of cerebral infarction in almost 30% of AD patients (18,19). In retrospective analyses, subjects meeting the neuropathologic criteria of AD and showing additional brain infarctions had poorer cognitive function and a higher prevalence of clinical dementia than those without brain infarctions (20).

Presently, hypertension is the best established vascular risk factor of AD. Observational longitudinal studies have demonstrated that elevated blood pressure levels are strongly associated with the

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Received Aug 12, 2010; revised Jan 20, 2011; accepted Jan 21, 2011.

long-term risk of dementia and cognitive impairment and that antihypertensive treatment is associated with a reduced risk of cognitive impairment and AD (21). So far, five large-scale, randomized, controlled trials on antihypertensive treatment with dementia as secondary end point have been conducted (22–26). All five trials observed significant reductions in primary cardiovascular outcomes but only the Systolic Hypertension in Europe trial reported a significant reduction of the incidence of dementia and AD in the treatment group (23). A biological marker that allows predicting the response to the effect of antihypertensive treatment on the risk of AD would be of high clinical relevance. Recent detailed reviews of biological markers of AD currently under investigation are given by Blennow *et al.* (27), Hampel *et al.* (28), and Zetzsche *et al.* (29).

Atrial natriuretic peptide (ANP), a member of the natriuretic peptide family, is involved in the regulation of several physiologic parameters, including natriuresis, diuresis, and lowering of arterial blood pressure by its vasodilatory activity. As the measurement of ANP is difficult because of its rapid clearance from circulation, a midregional fragment of the precursor hormone, termed midregional proatrial natriuretic peptide (MR-proANP), can be detected as an inactive surrogate molecule of mature ANP (30). Midregional proatrial natriuretic peptide has been considered as a novel blood-based biological marker for circulatory function (30) and has been shown to be associated with blood pressure (31).

We have previously found that MR-proANP levels are significantly increased in AD patients compared with healthy elderly control subjects (32). Furthermore, we showed that increased MR-proANP plasma levels are able to predict conversion from predementia MCI to manifest AD, representing an independent risk factor for conversion to AD in patients below the age of 72 (33).

In the present study, we investigated whether MR-proANP plasma levels predict the effect of antihypertensive treatment on rates of conversion and cognitive decline in subjects with MCI in an observational study. We hypothesized that in patients with increased MR-proANP levels, circulatory dysfunction would have a higher contribution to cognitive decline, and therefore, these subjects would show higher benefit from treatment with antihypertensive drugs.

Methods and Materials

Patients

In the present study, we included MCI patients previously recruited at the Memory Disorder Clinic at Malmö University Hospital, Sweden, between July 1998 and June 2001 for the cerebrospinal fluid biomarker study by Hansson *et al.* (34). The study was approved by the local ethical review board at Lund University, Sweden, where the study was conducted. Analyses of MR-proANP were done from saved samples and were covered by a general permission from the local ethical review board at Lund University for analysis of markers involved in vascular dysfunction and inflammation. All analyses were covered by obtained informed consent. One hundred thirty-four MCI patients were followed for up to 6 years. Patients and clinical characteristics were described earlier in detail by Hansson *et al.* (34). Treatment was neither randomized nor related to the study but documented in a standardized manner at study entry. In total, 47 patients received antihypertensive treatment ($n = 26$ beta blockers, $n = 21$ diuretics, $n = 13$ calcium receptor antagonists, and $n = 11$ angiotensin-converting enzyme inhibitors or angiotensin II type 1 blockers.

Procedures

Experienced physicians specialized in cognitive disorders undertook physical, neurological, and psychiatric examinations; careful clinical history (e.g., presence of heart disease of any kind, presence of heart failure); and functional assessment of the patients. The diagnosis of heart failure had been taken from the patients' medical records as part of our general characterization of patients and was not made by ourselves. Blood pressure was measured in a sitting position after patients had been in a sitting position for at least 15 minutes. Blood was taken at the Malmö University Hospital between 8:00 AM and noon. Patients were not fasting. Blood was collected in tubes containing ethylenediaminetetraacetic acid as anticoagulant and centrifuged at 2.000*g* for 10 minutes at +4°C. The supernatant was pipetted off. Plasma samples were frozen at –80°C and sent on dry ice to Germany (B.R.A.H.M.S. Aktiengesellschaft [AG], Hennigsdorf, Germany) for further analysis.

Analysis of MR-ProANP

Midregional proatrial natriuretic peptide was assessed using a novel sandwich immunoassay (MR-proANP luminescence immunoassay) (B.R.A.H.M.S. AG) as described in detail elsewhere (30). The functional assay sensitivity (defined as interassay coefficient of variance $< 20\%$ for all concentrations above the given value) is 20 pmol/L. In previous investigations, median MR-proANP in 325 healthy individuals was 45 pmol/L (95% confidence interval 43–49 pmol/L) (30).

Statistical Analysis

Conversion from MCI to probable AD or other types of dementia was studied using Cox regression analysis and time-dependent receiver operating characteristic and area under the curve analysis. Multivariable Cox regression analysis was performed to adjust the evaluation of treatment and biomarker interaction for age, gender, apolipoprotein E (APOE) $\varepsilon 4$ carrier status, and blood pressure, as well as heart failure and heart disease for the extended analysis, and to model censoring effects on the outcome conversion. Interaction terms for age, treatment, and MR-proANP were included. Age, MR-proANP ($\log_{10}$ transformed), and blood pressure were treated as continuous variables, while treatment, gender, APOE $\varepsilon 4$ carrier status, heart failure, and heart disease were treated as categorical variables. Patients developing other forms of dementia were censored at the time of conversion.

Kaplan-Meier curves of times to progression to probable AD (pAD) and hazard ratios between treated and untreated patients in different subgroups were calculated to illustrate the results from the multivariable Cox regression analysis. Differences between groups were tested using the log rank test.

For the simplified categorized analysis, Fisher's exact test for 2×2 classification tables was used to compare conversion to pAD rates for treated and untreated patients. Patients with other forms of dementia were counted as not converted to AD.

Student *t* test was applied for comparing the change in Mini-Mental State Examination (MMSE) between treated and untreated patients. A p value of .05 was considered significant. No p values were adjusted for multiple testing. All statistical analyses were performed using R version 2.5.1 (http://www.r-project.org).

Results

Patient and group characteristics, including MR-proANP values, are shown in Table 1. Detailed characteristics were already presented elsewhere (34). Midregional proatrial natriuretic peptide values ranged from 20 to 323 pmol/L, with the median at 99.5 pmol/L, the 75th percentile at 130 pmol/L, and the 95th percentile at 227 pmol/L.

Baseline MR-proANP was associated with conversion to pAD ($p < .0001$, area under the curve at 6 years for prognosis of conver-