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VASCULAR RISK FACTORS AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE: THE CACHE COUNTY STUDY

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Abstract

Objective—Knowledge of potentially modifiable risk factors for neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) is important. This study longitudinally explores modifiable vascular risk factors for NPS in AD.

Methods—Participants enrolled in the Cache County Study on Memory in Aging with no dementia at baseline were subsequently assessed over three additional waves, and those with incident (new onset) dementia were invited to join the Dementia Progression Study for longitudinal follow-up. 327 participants with incident AD were identified and assessed for the following vascular factors: atrial fibrillation, hypertension, diabetes mellitus, angina, coronary artery bypass surgery, myocardial infarction, cerebrovascular accident, and use of antihypertensive or diabetes medicines. A vascular index (VI) was also calculated. Neuropsychiatric symptoms were assessed over time using the Neuropsychiatric Inventory (NPI). Affective and Psychotic symptom clusters were assessed separately. The association between vascular factors and change in NPI total score was analyzed using linear mixed model and in symptom clusters using a random effects model.

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Results—No individual vascular risk factors or the VI significantly predicted change in any individual NPS. The use of antihypertensive medications more than four times per week was associated with *higher* total NPI and Affective cluster scores.

Conclusions—Use of antihypertensive medication was associated with higher total NPI and Affective cluster scores. The results of this study do not otherwise support vascular risk factors as modifiers of longitudinal change in NPS in AD.

Keywords

dementia; Alzheimer's; neuropsychiatric; vascular

INTRODUCTION

Neuropsychiatric symptoms (NPS) such as depression, delusions, anxiety and agitation affect up to 90% of all patients with Alzheimer's disease (AD) over the course of their illness (Tariot *et al*., 1995; Steinberg *et al*., 2008). NPS have been linked to greater caregiver and patient distress (Rabins *et al*., 1999; Craig *et al*., 2005; Gonzalez-Salvador *et al*., 1999), increased cost of care (Finkel, 2000; Beeri *et al*., 2002), more rapid cognitive and functional decline (Palmer *et al*., 2011; Rosenberg *et al*., 2012), and worse quality of life (Banerjee *et al*., 2009; Black *et al*., 2011). Given the high prevalence of NPS, as well as their consequences, understanding what contributes to their occurrence in AD is sorely needed.

Various factors have previously been found to modify risk of NPS (Treiber *et al*., 2008) Older age, sleep disturbance, white matter disease, and lacunes in the right basal ganglia have been associated with an increased risk of depression (O'Brien *et al*., 2000; Arbus *et al*., 2011; Casanova *et al*., 2011; Palmqvist *et al*., 2011). Older age and increased cognitive and functional impairment increases risk of apathy (Starkstein *et al*., 2001; Boyle *et al*., 2004; Starkstein *et al*., 2006), and older age, lower premorbid agreeableness, and increased cognitive and functional impairment may increase the risk for agitation and aggression (Holtzer *et al*., 2003; Copeland *et al*., 2003 Tsai *et al*., 1996; Archer *et al*., 2007). Psychotic symptoms, meanwhile, have been associated with worse cognitive or functional impairment, older age, and lacunes in the left basal ganglia (Harwood *et al*., 1999; Harwood *et al*., 2000; Bassiony *et al*., 2000; Paulsen *et al*., 2000; Mizrahi *et al*., 2006; Palmqvist *et al*., 2011). Anxiety and aberrant motor behavior have been associated with white matter disease (Berlow *et al*., 2010).

No consistently effective pharmacological treatment is available for any NPS in dementia (Sink *et al*., 2005; Schneider *et al*., 2006). Treatment of psychosis and agitation with antipsychotics is associated with significant safety concerns, including mortality (Kales *et al*., 2007; Gill *et al*., 2007). Although some previous research has found antidepressants to be effective in treating depression in AD (Lyketsos *et al*., 2003; Rao *et al*., 2006), recent larger studies demonstrate no benefit vs. placebo (Weintraub *et al*., 2010; Banerjee *et al*., 2011). The efficacy of non-pharmacological treatments (e.g. psychosocial interventions) also remains inconclusive (Jeste *et al*., 2008). Given the enormous burden of NPS on patients and caregivers and limited treatment options, knowledge of *potentially modifiable* risk factors for NPS in AD is important. As noted by Treiber et al. (2008), vascular factors, such as hypertension, stroke and hyperlipidemia, are of particular interest because they are common in the elderly and associated with NPS among individuals without AD. In a cross-sectional sample of 254 participants with AD followed in the Cache County Study on Memory in Aging (CCSMA), stroke prior to onset of AD was associated with a 3–4X increased risk for delusions, depression, and apathy; hypertension with 2–3X increased risk for delusions, anxiety, and agitation/aggression (Treiber *et al*., 2008). The CCSMA and associated Dementia Progression Study (DPS) have followed a cohort of participants with

AD for up to 11 years and provide the opportunity to longitudinally examine the interaction between vascular risk factors and NPS. Mielke et al. (2007), for example, studied 135 individuals from this cohort with incident AD and found atrial fibrillation, systolic hypertension, and angina to be associated with a faster rate of AD progression. Our study is, to our knowledge, the first to longitudinally explore modifiable vascular risk factors for NPS in AD.

METHODS

Sampling and screening

The (DPS) (Tschanz *et al*., 2011) longitudinally followed participants with incident dementia who had been identified through their enrollment in the population-based CCSMA. The methods of the CCSMA have been reported elsewhere (Breitner *et al*., 1999; Lyketsos *et al*., 2000). Briefly, we approached all permanent residents of Cache County, Utah, who were 65 years or older (n= 5,677) and enrolled 90% (n= 5,092). Participants were screened using an adaptation of the modified Mini Mental State Examination (3MS) (Tschanz *et al*., 2002), and those who screened positive, along with a weighted, stratified population subsample, were studied further using an informant based telephone interview (Kawas *et al*., 1994). Those whose interviews were suggestive of probable or possible dementia underwent a comprehensive assessment including an in depth history with a knowledgeable informant and neuropsychological testing, including Mini-Mental State Examination (Folstein *et al*., 1975). A psychiatrist and neuropsychologist reviewed assessment data, and those with suspected dementia were asked to undergo neuroimaging, laboratory studies and examination by a psychiatrist. The comprehensive assessment was repeated at 18 months to confirm initial dementia diagnosis with longitudinal data.

Procedure

Dementia diagnoses were assigned by a panel of experts in neurology, geropsychiatry, neuropsychology and cognitive neuroscience who reviewed all available data. AD was diagnosed by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann *et al*., 1984). The participants with no dementia at baseline were subsequently re-assessed over the course of 3 additional waves, and those incident (new-onset) dementia were invited to join the DPS (Figure 1) for longitudinal follow-up. The studies were approved by the institutional review boards of Duke University Medical Center, Johns Hopkins University, and Utah State University.

Assessment of Neuropsychiatric Symptoms

The NPI version used in the CCSMA and DPS (Cummings *et al*., 1994) assesses ten categories of neuropsychological symptoms: delusions, hallucinations, agitation/aggression, depression, apathy, elation, anxiety, disinhibition, irritability, and abnormal motor behavior (e.g., wandering, pacing). The NPI examines whether symptoms have occurred over the past month. Symptoms are ascertained by a trained examiner via a structured interview with a caregiver. If a symptom is endorsed, the respondent is asked to rate its frequency on a four-point scale and severity on a three-point scale, which when summed across domains produces an NPI *total* score. Multiplying the frequency and severity scores yields a domain score ranging from 1–12. Based on prior research (Lyketsos *et al*., 2001), the presence of Affective cluster symptoms was defined here as >0 score on any one of the depression, anxiety or irritability domains, and the presence of Psychotic cluster symptoms as >0 score on either the hallucination or delusion domains.

Assessment of Vascular Factors

Based on information obtained up to the visit at which the subject was diagnosed with dementia (baseline), it was determined whether the participants had a history of the following vascular factors: atrial fibrillation (AF), hypertension (HTN) (defined as lifetime history of diagnosed HTN determined via self-report interview prior to the diagnosis of dementia), diabetes mellitus (DM), angina, coronary artery bypass surgery (CABG), myocardial infarction (MI), and cerebrovascular accident (CVA). Systolic blood pressure (SBP) was assessed as a continuous variable. Participants were assessed for ever having taken antihypertensive medications and diabetes mellitus medications. In addition, a Vascular Index (VI) was calculated. This VI was identical to one used in a previous study of vascular risk factors in the CCSMA and DPS (Mielke *et al*., 2007), which in turn was adapted from the stroke risk profile of the Copenhagen City Heart Study (CCHS) (Truelsen *et al*., 1994). As noted by Mielke *et al*., (2007), two modifications of the VI from the CCHS were made: left ventricular hypertrophy was excluded because this information was not obtained in the CCSMA, and age was excluded to study its effect as a potential confounder or modifier. Using the same point system as the CCHS, the VI includes the following variables: AF, HTN (SBP> 160), DM, smoking, cardiovascular disease (CVD) (defined as history of MI, angina, or CABG), and current antihypertensive use. For nursing home patients, this medication information was obtained from medication administration records. The VI is described in more detail in Mielke *et al*., 2007. Participants were categorized as anti-hypertensive users if at the baseline visit they took medications from any of the following drug classes >= 4 times weekly: angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics.

Data analysis

We used linear mixed effects models to examine the effects of vascular factors and VI on average change in the log of the total NPI score over time. The data were log transformed due to the highly positive skew of the distribution to help meet the assumptions of the linear mixed model. These models included both random intercepts and random effect for time of follow-up. Individual effects were assessed using model-based *t* and *F* tests. Due to the nature of the trajectory, a quadratic effect of time (time-squared) was included in models predicting total NPI score (Tschanz *et al*., 2011), and to examine the association of each predictor with *rate of change in NPI*, interactions between predictors and time and time-squared were tested. Other potentially confounding factors (including sex, education level, age at onset, dementia duration, and APOE genotype) were likewise included and examined. We examined the presence of cluster symptoms (i.e., presence/absence of affective and psychotic symptoms, respectively) over time using logistic regression models, with random effects for time. Models were evaluated primarily with respect to VI, time, and the interaction between the two in order to assess the differential effects of vascular index on the average odds of affective or psychotic symptoms over time. All variables, including the additional confounding factors mentioned above, were examined using model-based chi-square and likelihood ratio tests for corresponding regression coefficients. Analyses were completed using SAS version 9.2.

RESULTS

The CCSMA identified 327 participants with new-onset AD who were then followed in the DPS. The baseline (i.e., at the time that AD was diagnosed) characteristics of these participants are in Table 1, and baseline NPI scores are in Table 2. Participants completed multiple study visits from 0.7 to 10.5 years from dementia onset. Sixty-three percent died during the study, and 3.3% either refused further follow-up or moved from the area. The mean (SD) duration of AD from onset to the time of last observation was 4.09 (2.87) years.

One hundred and five (32%) participants had no follow-up assessments after the baseline visit, of which 60 (57%) were lost due to death, 37 (35%) either refused or died after moving and the rest were pending a subsequent follow-up visit. Compared to those who completed at least one follow-up, these 105 were significantly older and scored lower on the MMSE and NPI total, but years of education and proportion of men and women did not significantly differ.

Fifty-one percent of participants had at least one neuropsychiatric symptom at baseline visit. The most common symptoms were depression (25%), apathy (17%), and irritability (17%); least common were elation (1%), hallucinations (5%), and disinhibition (7%).

Examining vascular factors as predictors of total NPI score, the following demonstrated no significant interaction with respect to time: VI (p= 0.93), AF (p= 0.70), SBP (p= 0.20), angina (p=0.44), MI (p=0.50), CABG (p= 0.14), diagnosed HTN ever or never (p= 0.96), and use of diabetes medications (p= 0.37). Unexpectedly, the use of antihypertensive medication 4 times per week or more was associated with higher total NPI scores (p= .03) and specifically greater risk of experiencing Affective symptoms (OR= 1.29, p= 0.05) compared to those not taking such medications. The plot of the total NPI score over time by antithypertensive group is displayed in Figure 2. Note that the effect of antihypertensives suggests higher NPI scores in the short term and does not appear to extend to longer follow-up periods. This is an issue that is difficult to examine in this sample due to sparseness of data with longer follow-ups. Note that for ease of interpretation, the raw total (and not transformed total) NPI scores are displayed. The probability plot for the odds ratio of the time*antihypertensive medication interaction for Affective symptoms is displayed in Figure 3. To address the question of whether higher total NPI score in the group using antihypertensives >4X weekly was due to the increase in affective score cluster, the total NPI scores excluding the affective domains were calculated, and the results were nearly identical. Vascular factors did not predict change in any individual NPI symptom over time.

DISCUSSION

In this longitudinal study of the relationship between vascular risk factors and NPS in a community-based AD cohort, we found no association between any individual vascular risk factor, or a cumulative vascular index, and the course of NPS. Our findings stand in contrast to our previous cross-sectional study by Treiber *et al*., (2008) using CCSMA prevalent and incident AD cases which showed a positive association at baseline between stroke prior to onset of AD and delusion, depression, and apathy, as well as a similar association between hypertension and delusions, anxiety, and agitation/aggression. Longitudinal analysis in the CCSMA (Tschanz *et al*., 2011), meanwhile, has demonstrated only marginal association between the rate of change of NPS and change in AD severity. Thus while vascular risk factors increase the likelihood of NPS being present (Treiber *et al*., 2008), as well as modulate the rate of AD progression (Mielke *et al*., 2007), the *course* of these NPS appears to occur largely independent of either vascular risk factors or disease progression. The potential benefits of modulating vascular risk factors in those with AD may therefore not extend to NPS.

In the current study, the use of antihypertensive medications more than 4 times per week was associated with higher rate of increase in total NPI score. Based on analyses to date for up to 6.2 years after baseline visit, which encompasses 95% of the collected data, these participants were also more likely to have Affective symptoms but not Psychotic symptoms. Hypertension can increase the risk of cerebrovascular disease, which has in turn been linked to increased incidence of depression in dementia (O'Brien *et al*., 2000; Lyketsos *et al*., 2000). However, no association was found in the current sample between the Affective

cluster and hypertension itself. These results differ from that of Bassiony *et al*. (2000) who found an association between antihypertensive use and psychotic symptoms. One possible explanation for our finding is that antidepressant side effects of antihypertensive medications (e.g., beta blockers) may increase the likelihood of depression symptoms. However, the relationship between beta blockers and depression has itself recently been called into question (Verbeek *et al*., 2011). The model type used in the analyses did not allow comparison between different classes of antihypertensive medications. Furthermore, these findings may represent a Type I error given the many analyses performed. With the application of a stringent Bonferonni correction, the new alpha would be p= .005, and none of the findings would meet that level of significance. The analysis in this study is exploratory, and replication in other samples is needed to determine whether the findings have implications in the clinical setting.

Although the results of this study do not support vascular risk factors as modifiers of NPS in AD, several limitations warrant consideration. First, because incident dementia was only ascertained every three years, participants with more rapidly progressing AD may have died prior to being assessed for NPS. Second, NPI subdomains were examined in terms of their presence or absence, and not by symptom severity. As noted by Treiber *et al*. (2008), most NPI disturbances in this cohort were in the mild range, limiting the power to assess the relationship between vascular factors and NPS severity. Finally, the CCSMA and DPS cohort is ethnically homogenous, and results may not generalize to other populations.

CONCLUSION

No clear relationship was demonstrated between vascular risk factor and NPS in AD in this longitudinally examined community-based cohort. However, given the severe burden of NPS in AD and limited treatment options available, further study of the effects of antihypertensive medications and modifiable risk factors in AD remains of interest.

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Key points

1. No individual vascular risk factor, nor a Vascular Index, significantly predicted change in any individual neuropsychiatric symptom in AD.
2. Use of antihypertensive medications more than four times per week was associated with higher total neuropsychiatric inventory (NPI) and Affective cluster scores in AD
3. Further study of the effects of antihypertensive medications and modifiable risk factors in AD remains of interest

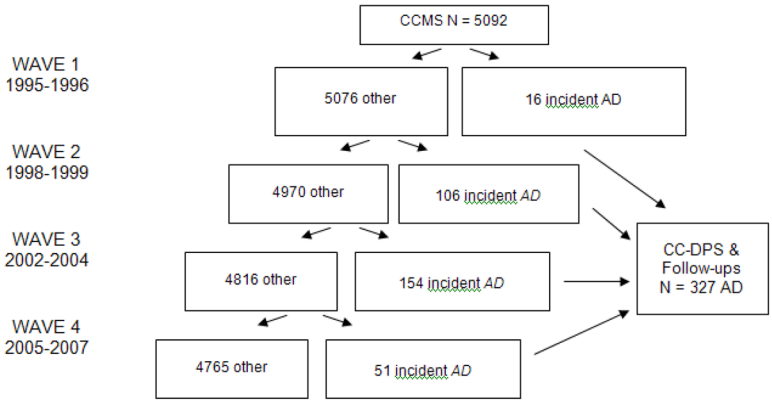

Figure 1.
Participants identified with AD in the CCSMA

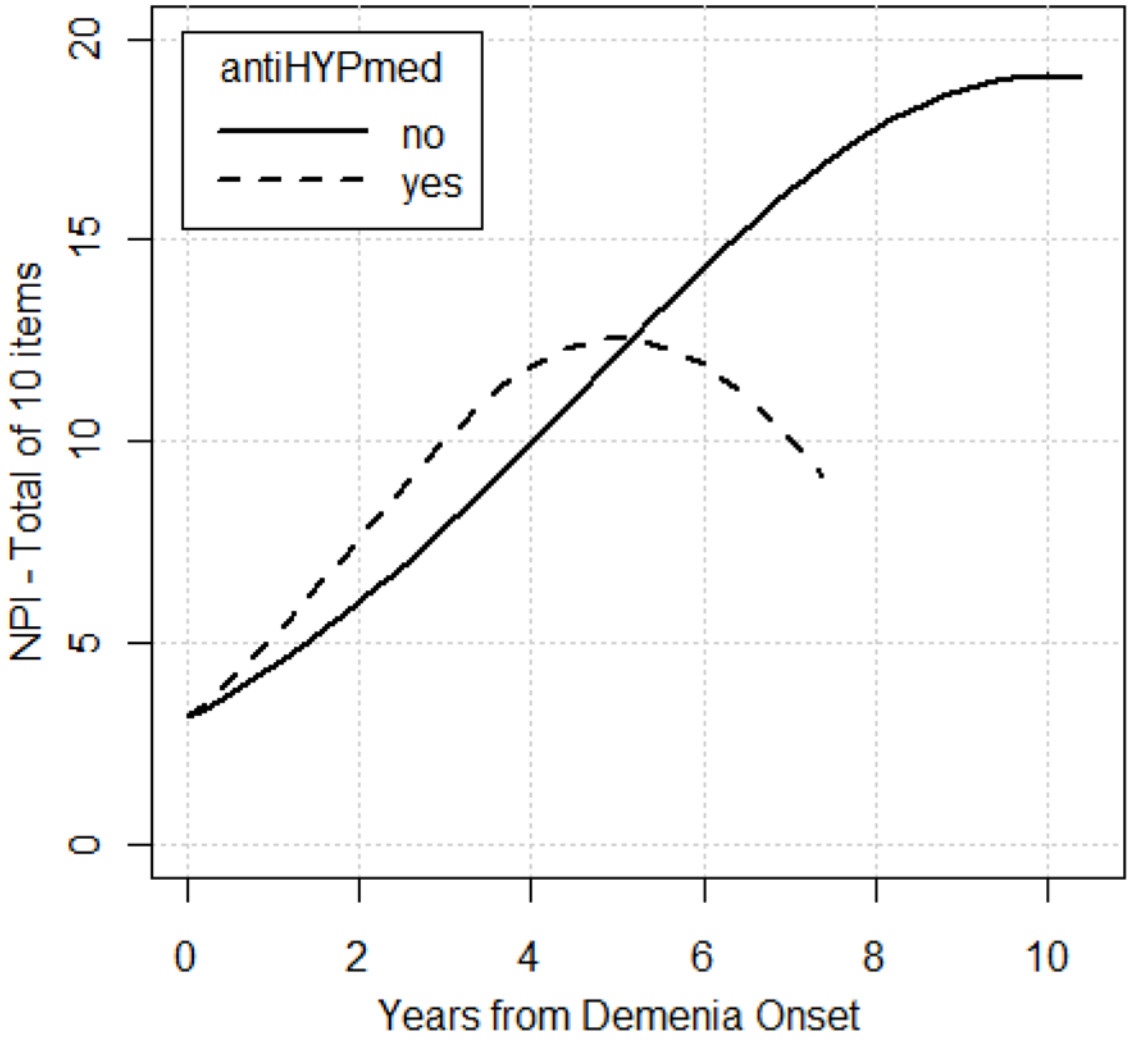

Figure 2.
displays the relationship between antihypertensive medication group and total NPI scores over time, plotted to the extent of follow-ups completed in each group. Note that estimates of total NPI scores beyond 7 years after dementia onset are based on 21 or fewer participants and therefore estimates may be less reliable from this point forward.

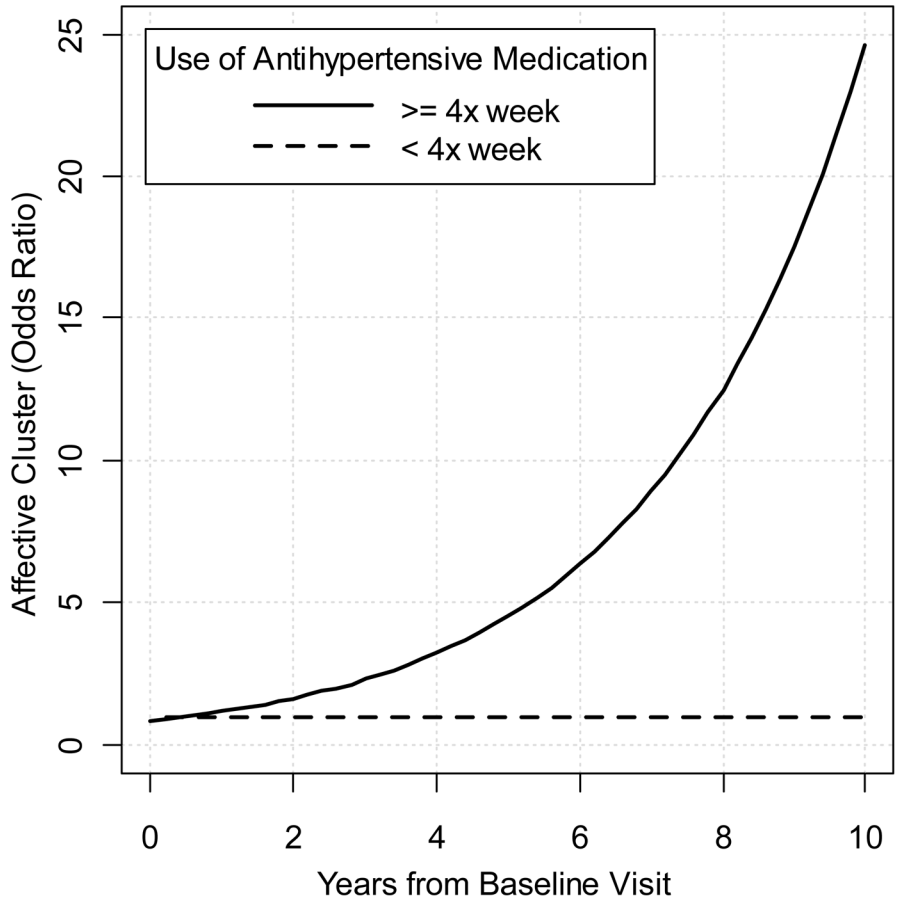

Figure 3.
displays the time dependant odds ratio comparing the presence of affective symptoms for the group taking antihypertensive medications (at least 4 times per week) compared to those either not taking antihypertensive medications or taking them at a lower frequency. Note that estimates of odds ratios beyond 7 years after dementia onset are based on 21 or fewer participants and therefore estimates may be less reliable from this point forward.

Table 1

Demographic and baseline characteristics

Male N(%)	113(35)
Female N(%)	214(65)
Age M(SD)	84.23 (6.46)
Years of education M(SD)	13.2 (3.0)
Caucasian M(SD)	324 (99)
Nursing home or locked unit N(%)	56 (17)
MMSE M(SD)	21.97 (4.59)
CDR M(SD)	1.05 (0.58)
GMHR	
Excellent N(%)	39 (12)
Good N(%)	179 (54)
Fair N(%)	107 (33)
Poor N(%)	2 (1)
Number follow-ups M(SD)	3.38(2.73)
Duration follow-ups M(SD)	5.09 (2.87)

Table 2

Baseline Neuropsychiatric Inventory (NPI) scores

Delusions N(%)	48(15)
Hallucinations N(%)	17(5)
Agitation/aggression N(%)	32(10)
Depression N(%)	78(25)
Apathy N(%)	54(17)
Elation N(%)	2(1)
Anxiety N(%)	42(13)
Disinhibition N(%)	21(7)
Irritability N(%)	55(17)
Aberrant Motor Behavior N(%)	27(9)
NPI any N(%)	162(51)
NPI total M(SD)	4.22(8,33)