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Risk Factors, Neuroanatomical Correlates, and Outcome of Neuropsychiatric Symptoms in Alzheimer's Disease

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Abstract

Background—An integrative model of neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) is lacking.

Objective—In this study, we investigated the risk factors, anatomy, biology, and outcomes of NPS in AD.

Methods—181 subjects were included from the Alzheimer's Disease Neuroimaging Study (ADNI). NPS were assessed with the Neuropsychiatric Inventory Questionnaire at baseline and 6 months. NPI >3 was used as a threshold for NPS positivity. Three NPS courses were characterized: 1) minimal/absent (negative at 0 and 6 months, $n = 77$); 2) fluctuating (positive only at one time point, $n = 53$); 3) persistent (positive at both time points, $n = 51$). We examined the association between NPS course and family history of dementia, personal history of psychiatric

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disorders, cerebrospinal fluid biomarkers, atrophy patterns, as well as longitudinal cognitive and functional measures at 12 and 24 months (MMSE, CDR-SOB, FAQ).

Results—AD subjects with absent, fluctuating, or persistent NPS had similar CSF amyloid- β and tau levels. AD subjects with minimal/absent NPS had less personal history of psychiatric disorders (35%) than those with fluctuating (57%; $p = 0.015$) or persistent NPS (47%, not significant). At 24 months, AD subjects with persistent NPS had worse cognitive (MMSE; $p = 0.05$) and functional (CDR-SOB; $p = 0.016$) outcomes. Dorsolateral prefrontal atrophy was seen in persistent NPS, but not in fluctuating NPS.

Conclusions—Our results suggest that individuals with personal history of psychiatric disorders might be more vulnerable to develop NPS throughout the course of AD. The worst cognitive and functional outcomes associated with NPS in AD underscores the importance of monitoring NPS early in the disease course.

Keywords

Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative; apathy; depression; neuropsychiatric inventory; neuropsychiatric symptoms; psychosis

INTRODUCTION

Although the clinical hallmarks of Alzheimer's disease (AD) are memory, executive, and other cognitive impairments, neuropsychiatric symptoms (NPS) are common and a major source of disability and distress [1]. Despite recent advances in understanding the genetic [2] and anatomic basis [3] and prognostic significance [4] of specific cognitive symptoms in AD, relatively little similar data exist for NPS, and a number of clinically important questions remain.

One critical question is, what makes some AD patients more likely to develop NPS than others? AD patients with depression have a higher prevalence of personal history of psychiatric symptoms and/or mood disorders [5, 6]. This association suggests a pre-existing (possibly complex genetic) vulnerability, whereby patients with a history early in life of a psychiatric disorder may be at greater risk for psychiatric symptoms during the course of AD. However, Ropacki and Jeste did not identify such an association with regard to psychosis [5]. Aside from these studies, very little investigation has been performed of factors that may confer increased vulnerability to NPS in AD dementia. Similarly, while the anatomical and functional changes associated with apathy and psychosis have been extensively studied [6, 7], less attention has been devoted to other behavioral disturbances seen in AD. Another highly clinically relevant question is, is outcome worse in AD patients with NPS? Several studies suggest that some specific behavioral disturbances predict worse cognitive and functional outcome in AD [5, 8–10]. Relations between long-term outcome and NPS other than agitation and psychosis have been less commonly investigated. AD patients who eventually develop psychosis have accelerated cognitive decline even before these symptoms. This suggests that the risk factors involved in behavioral disturbances of AD, which could potentially be inherited, might also be involved in cognitive decline [11, 12]; alternatively, the presence of NPS or their treatment might accelerate cognitive decline.

The main objective of the present study was to investigate the characteristics of mild AD dementia subjects who have any type of NPS to determine whether such subjects differ in risk factor profiles, neuroanatomy, molecular markers, and two-year outcome (both cognitive and functional). Our second objective was to assess whether NPS themselves—independent of their associated risk factors and demographic variables identified through the previous sets of analyses—are predictive of more rapid cognitive/functional decline.

METHODS

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.ucla.edu>). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see <http://www.adni-info.org>.

As part of the protocol, all subjects underwent thorough clinical and cognitive assessment including the Mini-Mental State Examination (MMSE) [13] and Clinical dementia rating scale (CDR) [14]. The diagnosis of AD was made if the subject had a MMSE score between 20 and 26, CDR score of 0.5 or 1, and met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD [15]. At screening, ADNI subjects did not have significant neurological conditions, did not have significant cerebrovascular risk factors (modified Hachinski Ischemic Score ≥ 4), and were not significantly depressed (Geriatric Depression Scale ≥ 5). Psychiatric exclusion criteria included severe psychotic symptoms within the past 3 months, any history of schizophrenia, a history of alcohol or substance abuse within the past 2 years, or active psychiatric disorder (such as major depressive disorder or bipolar disorder) within the past 1 year. Subjects could be on stable dose of antidepressants lacking significant anticholinergic side effects. Other psychoactive medication had to be washed out at least 4 weeks prior to screening. AD subjects were followed up at 6, 12, 24, and 36 months post baseline assessment.

Standard protocol approvals, registrations, and patient consents

This study was approved by institutional review boards of all participating institutions and written informed consent was obtained from all participants or authorized representatives according to Good Clinical Practice, the Declaration of Helsinki and U.S. 21 CFR Part 50-Protection of Human Subjects, and Part 56-Institutional Review Boards.

Neuropsychiatric status

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q) [16]. The NPI-Q covers 12 different domains (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, aberrant motor behavior, disinhibition, irritability, sleep, and eating). In each domain, the informant rates the presence/severity of symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe) for a maximum total score of 36. We dichotomized AD subjects as NPS-positive and NPS-negative based on a NPI cutoff score ≥ 4 , which has been previously used and validated as the cutoff for clinically significant NPS in prior clinical trials and observational studies [17, 18]. Based on longitudinal studies on NPS in AD—which consistently report that symptom frequency at any point in time underestimate the cumulative one-year frequency of NPS [18–21], we chose to consider the NPS summary score at two time points (baseline and 6 months) to categorize AD subjects into one of three groups. The first group consisted of subjects with persistent NPS: NPS global score ≥ 4 at baseline and 6 months. The second consisted of subjects with minimal/absent NPS: NPS global score <4 at baseline and 6 months. The third group consisted of subjects with fluctuating NPS: NPS global score ≥ 4 at baseline and <4 at 6 months or NPS global score <4 at baseline and ≥ 4 at 6 months. This grouping was established *a priori* to account for heterogeneity in NPS. In other neuropsychiatric syndromes such as schizophrenia, persistent versus fluctuating NPS may have both etiological and prognostic significance [22, 23]. To our knowledge, this type of a classification has not been used previously in studies of NPS in AD.

Risk factors

Data were analyzed on the following potential risk factors and biomarkers: 1) family history of dementia and AD, 2) personal history of psychiatric disorders, 3) apolipoprotein E (APOE) genotype (presence of at least one $\epsilon 4$ allele), 4) cerebrospinal fluid (CSF) amyloid- β_{1-42} , and 5) total tau levels.

Magnetic resonance imaging and morphometry

For each patient, 2 high-resolution structural T_1 -weighted MP-RAGE images were acquired either on a 1.5T General Electric Healthcare, a 1.5T Siemens Medical Solutions or a 1.5T Phillips Medical System scanner. Acquisition parameters were as follows: TR 2400 ms, TE minimum full time excitation, FA 8° , TI 1000 ms, voxel size $1.25 \times 1.25 \times 1.2$ mm. These data have been made available to the scientific community (<http://www.loni.ucla.edu/ADNI/>).

T_1 image volumes were examined quantitatively by a cortical surface-based reconstruction and analysis of cortical thickness using FreeSurfer version 4.5 (<http://surfer.nmr.mgh.harvard.edu>). The general procedures for this processing method have been

described in detail and applied and validated in a number of publications; the technical details can be found in select manuscripts [24, 25]. FreeSurfer processing of each brain MRI was visually co inspected and manually edited if errors were detected. We focused on the following ROIs: orbitofrontal prefrontal cortex, dorsolateral prefrontal cortex, hippocampus, amygdala, precuneus, insula anterior cingulate cortex, and posterior cingulate cortex.

Outcomes

The cognitive and functional outcomes studied here were the decline in MMSE, CDR Sum-of-boxes (CDR-SOB) scores, and Functional Assessment Questionnaire (FAQ) over 12 and 24 months.

Statistical analyses

All statistical analyses were performed with SPSS 19 (IBM, Armonk, NY). Analyses of variance (ANOVA) and chi-square analyses were used to compare groups on quantitative continuous and on categorical demographic variables respectively. The association between NPS groups and family history of dementia/AD and personal history of psychiatric disorders and APOE genotype was tested with the Chi-square test. Differences in CSF amyloid- β_{1-42} and total tau among the three groups were studied with ANOVA.

For the neuroanatomical data, age was entered into all models as a covariate since preliminary analyses indicated a trend-level relationship with NPS groups. Volumes of white matter hyperintensities were compared with analysis of covariance (ANCOVA). Statistical surface maps were generated by computing a general linear model for the effect of NPS groups on cortical thickness at each point. A Statistical threshold of $p < 0.05$ uncorrected for multiple comparisons was applied.

Finally, differences between NPS groups in cognitive (MMSE) and functional (CDR-SOB and FAQ) outcomes were assessed with ANOVA. To test whether NPS themselves— independent of their associated risk factors and demographic variables identified through the previous sets of analyses (MMSE decline, family history of AD and dementia, personal history of psychiatric disorders, CSF biomarkers)—are predictive of more rapid cognitive/ functional decline we used a series of linear regression analyses. Alpha for all tests of statistical significance was set at $p < 0.05$ (2-sided).

Hypothesis testing

Our first sets of hypotheses were that AD subjects with persistent and fluctuating NPS have a different risk factor profile than AD subjects with minimal/absent NPS. We first hypothesized that AD subjects with persistent and fluctuating NPS have more personal history of psychiatric disorders [26]. Previous studies suggested that genetic and/or neurobiological factors involved in psychiatric disorder might contribute to the risk of AD [27] and cognitive decline [11]. Therefore, we extrapolated that AD subjects with persistent or fluctuating NPS would have less history of the genetic and/or neurobiological risk factors associated with AD and hence less family history of dementia and AD and lower likelihood of an APOE $\epsilon 4$ allele. We hypothesized that NPS groups would not differ in their levels of CSF amyloid- β_{1-42} or total tau [28].

Based on a literature review of studies of primary psychiatric disorders with persistent/chronic NPS, we hypothesized that AD subjects with persistent NPS would have higher volume of white matter hyperintensities [29], frontal cortical atrophy (dorsolateral, medial, and anterior cingulate) [30, 31], and hippocampal atrophy [32] in comparison to AD subjects with fluctuating and minimal absent NPS. We also hypothesized that fluctuating NPS would have no neuroanatomical differences in comparison to AD subjects with minimal/absent NPS [33, 34].

Finally, we hypothesized that AD subjects with persistent NPS would experience more rapid cognitive and functional decline and that more rapid functional decline would be partially independent of cognitive decline (reflecting additional functional impairment due to psychiatric symptoms). We hypothesized that cognitive and functional decline would be related to NPS themselves rather than risk factors for NPS (biomarkers, family history of AD and dementia, personal history of psychiatric disorders).

RESULTS

Of the 193 AD subjects constituting the ADNI cohort at baseline, 181 completed both baseline and 6-month NPI-Q: 77 subjects were classified as minimal/absent NPS, 53 as fluctuating NPS, and 51 as persistent NPS. Irritability, apathy, anxiety, and depression were the most prevalent NPS among the total sample (39%, 34%, 34%, and 33% of the sample, respectively); hallucinations and euphoria were the less prevalent (6% and 5%, respectively; see Fig. 1), consistent with previously published population-based studies [10, 18]. Despite not crossing the NPI <4 cutoff, NPI scores of AD subjects with persistent NPS could markedly fluctuate from 0 to 6 months ([0–14] NPI points fluctuation, 3.37 in average; see Fig. 3). Subjects who completed the 6-month follow up were similar at baseline to those who did not ($n = 12$) for demographic variables gender, age, and education and for clinical variables CDR-SOB and NPI-Q total score. However, they had higher MMSE score (23.4 [2.0] versus 22.2 [2.5]; $F_{1,191} = 4.221$; $p = 0.041$). 79/181 subjects (44%) took some form of psychiatric medication (75 on selective serotonin reuptake inhibitors [SSRI], 10 on hypnotics [trazodone, zolpidem], 9 on non-SSRI antidepressants [bupropion, duloxetine, tricyclic antidepressants], 3 on benzodiazepines, and 3 on antipsychotics; some subjects took medication from more than one category). AD subjects with minimal/absent NPS took less psychiatric medication (27%) than those with fluctuating (57%) and persistent NPS (53%).

At baseline, NPS groups (minimal/absent-fluctuating - persistent) were similar for gender (M/F: 37/40 – 28/25 – 31/20; $\chi^2 = 2.00$; $p = 0.368$), age (76.5 [7.6] – 76.0 [7.9] – 74.0 [7.0]; $F_{2,178} = 1.75$; $p = 0.177$), and education (14.3 [3.1] – 15.5 [2.7] – 14.7 [3.4]; $F_{2,178} = 2.179$; $p = 0.116$). They were similar for MMSE scores (23.6 [1.9] – 23.0 [2.0] – 23.7 [2.1]; $F_{2,178} = 1.671$; $p = 0.191$) but differed on CDR-SOB (3.8 [1.7] – 4.5 [1.4] – 4.7 [1.7]; $F_{2,178} = 6.091$; $p = 0.003$) and FAQ (11.0 [7.1] – 13.6 [5.9] – 15.2 [6.6]; $F_{2,178} = 6.596$; $p = 0.002$). The demographic and clinical characteristics of the sample are presented in Table 1.

Subjects with persistent NPS had less familial history of dementia (29%) than those with fluctuating (55%; $\chi^2 = 6.819$, $p = 0.009$) or minimal/absent NPS (44%; n.s.), despite having similar influence of APOE $\epsilon 4$ genotype (65% with at least one allele versus 68% and 68%,

respectively). Conversely, AD subjects with minimal/absent NPS had less personal history of psychiatric disorders than those with fluctuating (57%; $\chi^2 = 5.915$, $p = 0.015$) or persistent NPS (47%, n.s.). NPS groups did not differ regarding their biomarker profile: number of APOE $\epsilon 4$ alleles (0/1/2 allele: 31/49/19 – 32/45/23 – 35/49/16; $\chi^2 = 0.940$, $p = 0.919$); CSF amyloid- β_{1-42} (141.6 [38.8] – 134.6 [31.1] – 152.5 [49.3]; $F_{2,97} = 1.190$; $p = 0.309$); total tau (125.5 [62.7] – 105.8 [45.6] – 122.7 [54.6]; $F_{2,97} = 1.427$; $p = 0.245$). *Post hoc* analyses showed a trend toward higher CSF amyloid- β_{1-42} in AD subjects with persistent NPS compared with AD subjects with fluctuating NPS.

Cortical atrophy varied between the NPS groups. In comparison with AD subjects with minimal/absent NPS, AD subjects with persistent NPS had more left and right dorsolateral prefrontal atrophy (superior frontal gyri). In comparison with AD subjects with minimal/absent NPS, AD subjects with fluctuating NPS had more atrophy of the left insula and less atrophy in the left and right medial parietal cortex (precuneus) (see Fig. 2). There was no association between NPS groups and white matter disease and hippocampal volumes.

163 AD subjects completed the 12-month evaluation and 138 subjects completed the 24-month evaluation. At 12 months, NPS groups did not differ on their MMSE decline ($F_{2,160} = 0.821$; $p = 0.442$) or progression of CDR-SOB ($F_{2,158} = 2.301$; $p = 0.104$) or FAQ scores ($F_{2,159} = 0.448$; $p = 0.640$). At 24 months, there was a significant difference between NPS groups for MMSE decline ($F_{2,133} = 3.052$; $p = 0.05$) and progression of CDR-SOB ($F_{2,132} = 4.284$; $p = 0.016$) but not for progression of FAQ scores ($F_{2,135} = 0.280$; $p = 0.757$) (see Fig. 3). In *post hoc* analyses, AD subjects with persistent NPS had worse MMSE decline in comparison with AD with minimal/absent NPS ($p = 0.016$) and worse functional (CDR-SOB) decline in comparison with AD with fluctuating NPS ($p = 0.015$) and minimal/absent NPS ($p = 0.007$). Controlling for MMSE decline, the association between NPS groups and CDR-SOB at 24 months was no longer significant ($F_{2,129} = 1.328$; $p = 0.269$). Controlling for family history of dementia and personal history of psychiatric disorders, NPS groups were still predictive of MMSE decline ($F_{2,129} = 3.874$; $p = 0.023$) and CDR-SOB progression ($F_{2,128} = 4.234$; $p = 0.016$) at 24 months.

DISCUSSION

In this study, we investigated the characteristics of participants with mild AD dementia who have any type of NPS to determine whether such patients differ in family history of dementia or personal psychiatric history, neuroanatomy and molecular markers, and two-year outcome (both cognitive and functional). We found that the baseline presence and early course of neuropsychiatric symptoms was associated with a specific risk factor profile, neuroanatomical correlates and cognitive and functional outcomes. AD subjects with persistent NPS had less frequent family history of dementia whereas AD subjects with fluctuating NPS had more frequent history of psychiatric disorders. AD subjects with persistent NPS showed more atrophy of the right and left prefrontal cortex compared to those with minimal/absent NPS whereas AD subjects with fluctuating NPS did not differ from the latter group. AD subjects with persistent NPS showed worse cognitive and functional outcome compared to AD subjects with fluctuating or minimal/absent NPS. This

association between NPS course and cognitive and functional outcomes was independent of risk factors for NPS (family history of dementia, personal history of psychiatric disorder).

The study also helps untangling pathophysiological mechanisms leading to NPS in AD. First, the fact that molecular markers of AD (APOE ϵ 4, CSF amyloid- β_{1-42} , total tau) were not associated with NPS symptoms in the present study suggests that NPS in AD may be at least partially independent from AD pathophysiology itself. Similar to cognitive variants of AD, behavioral expression of AD may be linked to genetically and environmentally mediated by selective vulnerability of frontal-subcortical brain circuits [35]. In that regard, previous studies have shown the psychosis in AD is associated with a distinct genetic profile [36–38]. The increased personal history of psychiatric disorders in AD subjects with fluctuating NPS evokes an alternative hypothesis whereby NPS would contribute to AD pathophysiology, perhaps through glucocorticoids-related alterations of hippocampal plasticity [39–41]. It is also possible that manifest or subclinical psychiatric conditions (personality, mood, anxiety, or psychotic disorders) are exacerbated by AD neuropathology through altered cognitive compensatory mechanisms and reduced insight. Finally, we cannot exclude that NPS in AD are the result of co-morbid pathologies, including vascular risk factors [42, 43] and traumatic brain injury [44]. Recent data suggest that vascular risk factors mediate the relation between psychiatric disorders (midlife depression) and AD [45] although this has not been found in other studies [46].

With regard to their neuroanatomical correlates, AD subjects with persistent NPS had more prominent prefrontal cortical atrophy in comparison to AD subjects with fluctuating or minimal/absent NPS. This finding also supports a possible relation between NPS and executive deficits in AD [47]. The dorsolateral prefrontal cortex is a key component of the well-known dorsolateral frontal-subcortical circuit, whose dysfunction is characterized primarily by executive deficits and motor programming abnormalities [48]. Dysfunction of frontal-subcortical circuits have been linked to NPS in AD [49–51] as well as a wide variety of primary psychiatric disorders [49, 52]. Interestingly, AD subjects with fluctuating NPS had relatively preserved right and left precuneus thickness but left insular atrophy compared with patients with minimal/absent NPS. Since these results had not been hypothesized and that we used a lenient statistical threshold, they should be interpreted cautiously. The precuneus is part of the default mode network and is involved in self-awareness [53] whereas the anterior insula is part of the salience network and is involved in affective processing including representations of feeling states [54, 55]. Additional investigation will be necessary to further interpret these results.

With regard to their cognitive and functional trajectories, AD subjects with persistent NPS demonstrated worse outcomes from those with fluctuating or minimal/absent NPS. This association was independent of the risk factors associated with NPS groups (family history of dementia, personal history of psychiatric disorders). It is possible that this is an effect of treatment of NPS, which may have cognitive side effects [56–58]. It is also possible that it may reflect non-compliance with standard treatment. These possibilities deserve further study.

Our study has limitations. First, the use of the NPI-Q, a caregiver version of the NPI, limits the reliability of NPS measurement. Ascertainment and quantification of behavioral disturbances are more reliably performed by clinicians using diagnostic interviews, and other more focused questionnaire-based instruments are also available for neuropsychiatric symptoms. Likewise, to our best knowledge, data on personal history of psychiatric disorders or familial history of dementia was obtained through self-report, which is not optimally reliable. Second, ADNI strict inclusion and exclusion criteria created selection bias by excluding the most severe NPS. Indeed, subjects with significant psychiatric impairment at the inclusion visit—including significant depression (Geriatric Depression Scale 5), psychotic symptoms within the past 3 months, any history of schizophrenia, or active psychiatric disorder (such as bipolar disorder) within the past 1 year—were excluded from the study. Furthermore, subjects who completed the 6-month follow up had slightly higher MMSE scores, which may lead to an underestimation of cognitive deterioration rates measured in this study.

Overall, this study suggests that persistent NPS in AD may represent a specific phenotype of the disease with a specific risk factor profile, neuroanatomical correlates and worse cognitive and functional outcome. Based on this preliminary observation, we believe that additional research on persistent NPS early in the course of AD dementia is warranted. For clinicians, these findings underscore the importance of assessment of NPS early in the course of the disease to try to identify, and potentially ameliorate, a poor prognostic indicator.

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Dr. Stéphane Poulin performed all statistical analyses. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Fig. 1. Baseline severity of NPI subdomains. Severity of the 12 Neuropsychiatric Inventory subdomains at baseline in subjects with persistent, fluctuating, and minimal/absent neuropsychiatric symptoms. Bars indicate mean and brackets indicate 95% confidence intervals.

Fig. 2. Neuroanatomical correlates of neuropsychiatric course in Alzheimer's disease. A) Persistent versus minimal/absent NPS. B) Fluctuating versus minimal/absent NPS. On the blue end of the spectrum, atrophy is more significant in persistent NPS and fluctuating NPS. On the red end of the spectrum atrophy is more significant in minimal/absent NPS.

Fig. 3. Longitudinal evolution of cognitive and functional measures in AD subjects with minimal, persistent and fluctuating neuropsychiatric symptoms. Spaghetti plots of longitudinal NPI, MMSE, CDR, and FAQ scores in AD subjects with minimal, persistent and fluctuating neuropsychiatric symptoms, and comparison of means with 95% confidence intervals. CDR, Clinical Dementia Rating (sum of boxes); FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

Table 1

Demographic and clinical characteristics of the patient groups

	Neuropsychiatric courses		
	Minimal/absent	Fluctuating	Persistent
Demographic variables			
Number (%)	77 (43)	53 (29)	51 (28)
Age, y (SD)	76.5 (7.6)	76.0 (7.9)	74.0 (7.0)
Sex, M/F	37/40	28/25	31/20
Education, y (SD) [†]	14.3 (3.1)	15.5 (2.7)	14.7 (3.4)
Personal and family history			
Family history of dementia (%) ^{*,§§}	44	55	29
Family history of AD (%) [*]	30	38	17
Personal history psychiatric disorder (%) [†]	35	57	47
Baseline clinical characteristics			
MMSE _{baseline} (SD)	23.6 (1.9)	23.0 (2.0)	23.7 (2.1)
MMSE _{6months} (SD)	22.9 (1.7)	21.8 (3.6)	22.0 (3.7)
CDR-SOB _{baseline} (SD) ^{†,††}	3.8 (1.7)	4.5 (1.4)	4.7 (1.7)
CDR-SOB _{6months} (SD) ^{†,††}	4.4 (1.8)	5.5 (2.6)	5.6 (2.1)
FAQ _{baseline} (SD) ^{†,††}	11.0 (7.1)	13.6 (5.9)	15.2 (6.6)
FAQ _{6months} (SD) ^{†,†}	13.4 (7.7)	16.8 (7.5)	16.7 (6.7)
Biomarkers profile			
APOE ε4 alleles, % with 0/1/2	31/49/19	32/45/23	35/49/16
Amyloid-β ₁₋₄₂ (SD)	141.6 (38.8)	134.6 (31.1)	152.5 (49.3)
Total tau (SD)	125.5 (62.7)	105.8 (45.6)	122.7 (54.6)

AD, Alzheimer's disease; CDR-SOB, Clinical Dementia Rating - Sum of Boxes; FAQ, Functional Assessment Questionnaire; MMSE, Mini-Mental State Examination; na, not available.

^{*} percentage excluding subjects for which information about family history was not available.

[†] $p < 0.05$;

^{††} $p < 0.01$: minimal/absent versus fluctuating;

[‡] $p < 0.05$;

^{‡‡} $p < 0.01$: minimal/absent versus persistent; $p < 0.05$; $p < 0.01$: fluctuating versus persistent.