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Biomarkers of basic activities of daily living in Alzheimer's disease

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Abstract

Functional impairment is common in Alzheimer's disease, and related to increased caregiver burden and institutionalization. There is a dearth of research investigating the relationship between specific biomarkers and basic activities of daily living such as toileting, feeding, dressing, grooming, bathing, and ambulating. The present study examined the relationship between serum based biomarkers and specific activities of daily living in a sample of Alzheimer's disease patients

Data were collected from 196 participants enrolled in the Texas Alzheimer's Research and Care Consortium Project and diagnosed with Alzheimer's. Basic activities of daily living were measured using the Lawton-Brody Physical Self-Maintenance Scale. A panel of 22 biomarkers previously found to be related to AD pathology was used for the analysis. Stepwise regression modeling was used to assess the link between the biomarkers and basic ADLs. Results were also examined by gender.

Nine of the 22 biomarkers were significantly related to basic ADLS. When stratified by gender, the biomarkers accounted for 32% of the variance in the male's scores and 27% in females. The pattern of significant biomarkers differed by gender with IL-7 and Tenascin C significantly related to basic activities of daily living for females and IL-15 significantly related to basic activities of daily living for males. The results of this study indicated that a small number of serum based biomarkers are related to basic ADLs, and these biomarkers differed by gender.

Keywords

Biomarkers; Alzheimer's disease; Basic Activities of Daily Living; Gender

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Introduction

Basic activities of daily living (BADLs), such as toileting, feeding, dressing, grooming, bathing, and ambulating are the primary self-care tasks required for independent functioning and are significantly impacted by Alzheimer's disease (AD) [1]. As cognitive deterioration progresses across the continuum of decline, patients with AD experience a gradual loss in BADLs [2]. Functional impairment in AD places a significant burden on caregivers [3] and is a leading cause of nursing home placement [4]. In fact, decline in activities of daily living ,both instrumental and basic, are the key characteristics used to distinguish Mild Cognitive Impairment (MCI) and AD[5] and are significantly related to the severity of AD [6]. Type and level of functional impairment are important features in the continuum from preclinical stages to AD [7].

Identification of biomarkers that are related to functional level in AD may provide clues into the pathophysiological features of such decline, which in turn, could lead to novel approaches for predicting progression as well as therapeutic approaches directly aimed at functional aspects of this disease. Although a number of studies have investigated the relationship between biomarkers and neuropsychiatric disorders, few have focused on the relationship of specific biomarkers to BADLs. A retrospective cohort study [8] investigated the relationship between ADLs and burden of neuritic plaques and neurofibrillary tangles at autopsy. These authors identified a significant relation between functional impairment and pathological burden, especially neuritic plaques within the medial temporal, occipital and orbital frontal regions. One study analyzing CSF and plasma biomarkers found no significant biomarkers of functional decline in AD [9]. In contrast, others have shown a significant relationship between low levels of plasma Aβ42 and C-reactive protein and functional decline in ADLS [10]. These markers accounted for approximately 12% of the variance in a measure of ADLs. An investigation of plasma inflammatory markers and a measure of total functional status found a significant relationship only with IL-6 and that for vascular dementia not AD [11].

In order to help clarify the relationship of biomarkers to functional ability, the present study investigated the relationship of a range of serum-based biomarkers to an overall measure of BADLs, as well as specific basic activities of daily living. A factor that may impact the nature of this relationship is gender. Our previous research [12] has pointed to the importance of gender differences in the relationship between cognitive functioning and functional behavior. We have also found significant gender differences in the biomarkers of depression in AD [13, 14]. Other research has shown gender differences in metabolic and genetic biomarkers [15] related to complex diseases such as AD and argues for the importance of stratifying by gender in analyzing biomarkers. Therefore, we also investigated the impact of gender on the relationship between biomarkers and BADLs in AD.

Materials and Methods

Participants

The total sample consisted of 196 (68 male, 129 female) community dwelling participants enrolled in the Longitudinal Research Cohort of the Texas Alzheimer's Research Consortium (TARC) who met criteria for probable AD. The methodology of the TARC project has been described in detail elsewhere [16]. Briefly, the TARC project is a longitudinal multisite study of a well-characterized cohort of AD patients, patients suffering from Mild Cognitive Impairment (MCI), and a group of normal controls. Each participant undergoes an annual evaluation that includes a medical examination, interview, neuropsychological testing, and blood draw. AD patients met consensus-based diagnosis for probable AD based on NINCDS-ADRDA criteria [17]. As dysfunction in ADLs is required

for a diagnosis of AD, the current study excluded normal controls as well as cases diagnosed with MCI. Demographic characteristics of the sample are presented in Table 1. The participants had a mean age of 77.41 years (SD= 8.291), a mean education of 13.98 years (SD= 3.538) and the mean MMSE score was 19.18 (SD= 6.222). Number of years of education was determined from self-report of the total number of years of education. The educational level of the sample is relatively high with the majority of the sample having at least a high school education. The MMSE suggests that the sample fell within the mild to moderate stage of cognitive decline . There were no significant differences between Males and Females for age (p= .169), education (p= .514) or MMSE score (p= .898). The majority of the participants were Caucasian (98%), with African American (1.5%) being the next largest group. The TARC project received Institutional Review Board approval and all participants and/or caregivers provided written informed consent.

Basic Activities of Daily Living

Information on BADLs was obtained from caregivers using the Lawton-Brody Physical Self-Maintenance Scale [18]. The scale consists of six categories of basic functions: Toileting; Feeding; Dressing; Grooming; Physical Ambulation and Bathing. Rating for each of the six items is done on a five-point likert scale which ranges from total independence to total dependence of function with higher scores indicating greater dependence. A total BADL score was derived by summing the scores from the six categories.

Biomarkers

The TARCC research platform utilizes biomarkers obtained using the Rules Based Medicine (RBM) humanMAP which assays over 152 serum-based protein biomarkers. The final panel selected consisted of 23 biomarkers included in the RBM humanMAP that have been related to AD pathology or disease progression. They were chosen based on prior research indicating their utility in differentiating normals from AD or having a relationship to functional decline. The ability of these biomarkers to consistently differentiate normals from AD or be differentially related to functional impairment in dementia suggests processes reflecting direct effects on the brain rather than acute phase or peripheral affects. The composition of the biomarker panel used in the current study was determined through a review of relevant literature and evaluation of biomarkers in the original TARCC biomarker panel used in the development of a serum-based test that differentiates AD from normal controls [19, 20]. . Twelve of the biomarkers appear in the TARCC predictive algorithm [20]: TNFα; Tenascin C; Fas Ligand; Fibrinogen; IL 5; IL 7; IL 10; Eotaxin; CRP; Stem Cell Factor; Ferritin and von Willebrand Factor . Eleven additional proteins were drawn from a review of biomarkers identified as being related to functional decline and available in the RBM humanMAP: Beta 2 microglobulin [21]; BDNF [22]; Complement 3 [23]; Factor VII [24]; IL 6 [25]; IL 8 [26]; IL12p40 [27]; IL 15 [28]; MMP3 [29]; TNF RII [30] and TNFβ [31]. IL-6 levels were measured, but were below the detectable range and were not included in the analysis, leaving a final panel of 22 biomarkers. Table 1 lists the biomarkers selected for inclusion. A number of the biomarkers under study are not normally distributed and in order to allow comparisons across biomarkers, all analyses were conducted using log transformed values of the biomarkers to approximate normal distributions.

Assays

Non-fasting blood samples were collected in serum-separating tubes during clinical evaluations, allowed to clot at room temperature for 30 minutes, centrifuged, aliquoted, and stored at −80°C in plastic vials. Batched specimens from either baseline or year-one follow-up exams were sent frozen to Rules Based Medicine (RBM, www.rulesbasedmedicine.com, Austin, TX) where they were thawed for assay without additional freeze-thaw cycles using the RBM multiplexed immunoassay human Multi-Analyte Profile (humanMAP). Individual

proteins were quantified with immunoassays using colored microspheres. Information regarding the least detectable dose (LDD), inter-run coefficient of variation, dynamic range, overall spiked standard recovery, and cross-reactivity with other humanMAP analytes can be readily obtained from RBM.

Data Analysis

Analyses of the data were performed using SPSS version 17.0. Stepwise regression modeling was used to evaluate the link between the biomarker panel and BADLs. The complete sample was first subjected to regression analysis and this was followed by separate analyses by gender. Independent variables for the regression analysis were the biomarkers and the dependent measures were total BADL score and scores on each of the six BADL items.APOE4 status, education and gender were co-varied. Analysis of variance was used to detect differences between genders on age, education, MMSE and total BADL score. Chi square analysis was used to assess gender differences in APOE4 status. Logistic regression was used to analyze the relationship between the biomarker panel and BADLs and a variable that dichotomized participants into those who were totally independent and those who required some level of assistance. The .05 level of significance was used for all analyses.

Results

Table 2 presents results of the regression modeling of significant biomarkers for total BADL score and each of the BADLs items for the complete sample. A total of 9 of the 22 biomarkers investigated were related to BADL total score or scores on the individual BADLs when analyzing the complete sample. As shown in Table 2, a relatively small number of biomarkers accounted for 36% of the variance in total score and 18.9%-32.2% of the variance in the six BADLs functions. The effects of APOE4 status, age and education were not significant for any of the regression models for the complete sample.

When the sample was analyzed following stratification on gender, different biomarker profiles emerged for Males (Table 3) and Females (Table 4). Regression analyses revealed that the significant biomarkers accounted for an average of 32.7% (range 19.2% - 42.4%) of the variance in the individual BADLs for Males and 27.5% (range 20.5% - 35.4%) of the variance for Females. The lowest adjusted R^2 was found for Ambulation for both genders.

Serum levels of IL-15 were negatively related to 5 of the 6 BADLs for Males. IL-15 was a significant biomarker for Females for two of the BADLs. Interestingly, unlike the finding for Males, levels of IL-15 were positively associated with BADL scores for Females. Lower levels of IL-15 were related to greater dependence for Males whereas increased levels of IL-15 were related to greater dependence for Females. Serum levels of IL-7 and/or Tenascin C emerged as significant biomarkers for all of the basic functions for Females but they were not significantly related to any of the basic functions for Males. The significant biomarkers are listed by gender in Figure 6. Five of the biomarkers: IL 15; IL 12p40; Complement 3 (C3); TNF RII and Fibrinogen appeared in significant regression equations for both genders. The biomarkers of BDNF, IL-10, Fas Ligand, TNFα and TNFβ were not significantly related to BADLs in either the complete sample or by gender.

A post hoc exploratory analysis using logistic regression, dichotomized participants into those who were totally independent and those who required some level of assistance. The biomarker profiles obtained in these analyses were similar to those found with linear regression. For Females, serum IL-7 and Tenascin C were significant biomarkers in 5 of the 6 functions and data regarding levels of these two biomarkers lead to correctly classifying an average of 77% (range 71% - 85%) of the participants. Ambulation was best predicted by level of CRP which correctly classified 64% of the cases. For Males IL-15 alone was a

significant predictor of 5 of the 6 basic activities leading to correctly classifying an average of 75% (range 65% - 81%) of the cases with TNF RII levels correctly classifying 70% of the cases for Ambulation.

Discussion

One of the purposes of the present study was to investigate the relationship between a panel of serum-based biomarkers that have been associated with AD and performance on basic activities of daily living. Analysis of the total sample of AD patients revealed that a relatively small number of biomarkers were able to account for a significant portion of the variance in BADLs. IL-7, Tenascin C and Complement 3 were significant markers of overall level of functioning for all of the basic activities assessed. Lower levels of IL-7 and higher levels of Tenascin C and Complement 3 were related to greater dependence. Increased Tenascin C is an inflammatory process response [32] and complement activation is a key component of neuro-inflammation [33]. Much as we found a relationship between increased Complement 3 levels in serum and lower levels of functioning on BADLs, previous research [33] has found CSF concentrations of Complement 3 negatively correlated with MMSE scores and CSF [34] levels of Complement 3 have been related to the level of cognitive impairment in a study of MCI and AD patients.

Among the other significant serum markers for the complete sample, an increased level of Beta 2 microglobulin (β2) was related to increased dependence, which is consistent with the work of Simonsen [35], who found β2 upregulated in AD and MCI. Higher serum levels of fibrinogen, which has been related to cognitive decline in MCI [36], was related in our study to increased dependence in Feeding for the complete sample, and to Feeding and Ambulation among Females. Higher levels of CRP were found to be significantly related to Grooming and Ambulation only for females. Prior research comparing CRP levels between normal controls and individuals with AD has produced conflicting results. Recent research [37] reported increased plasma levels in AD compared to normal controls and our group [38] observed decreased levels of serum CRP in among AD relative to normal controls, even though higher levels of CRP were related to more advanced disease severity among AD cases. It is interesting that the relationship between CRP and any of BADLs held only for females. This finding is consistent with our prior work documenting gender differences in a number of factors related to AD. Lower serum IL-8 levels have been found in MCI and AD compared to normal controls and has been shown to be negatively related to functional status in AD [39]. In our study, lower serum IL-8 levels were related to increased dependence for Grooming in the total sample and for Females and Ambulation in Males. These findings suggest the importance of gender as a factor in the pattern of biomarkers and BADLs.

When the analyses were conducted stratifying by gender , distinct biomarker profiles related to BADLs emerged. Five of the biomarkers were significant for BADL scores among both genders, although the direction of the relationship for IL-15 differed by gender. The distinct biomarker profiles for Males and Females show different major contributors to the variance accounted for in BADLs. For Males, IL-15 alone was a significant biomarker in Total BADL score (Adjusted $R^2 = 0.259$; $F= 24.062$, $p< 0.001$) and each of the functional behaviors (Mean Adjusted $R^2 = 0.229$; Range 0.182 - 0.299). For Females, IL-7 alone was a significant biomarker for Total BADLs score (Adjusted $R^2 = 0.115$; $F= 17.604$, $p< 0.001$) and Toileting, Feeding and Dressing (Mean Adjusted $R^2 = 0.102$; Range 0.096 - 0.114). Tenascin C and IL-7 were significant biomarkers for Total BADL and five of the six functional behaviors. When the effect of Tenascin C was added to that of IL -7, the two biomarkers together accounted for an average of 16.15% of the variance in the individual functional behaviors (Range 11.4% - 22.9%).

The current study has a number of limitations, the most important being the cross-sectional nature of the study. The TARC cohort is followed annually and the link between these baseline measures and change in BADLs is now being investigated. The TARC cohort is relatively well-educated which may affect the generalizability of the findings. Another possible limitation is that the sample is composed of cases that met criteria for "Probable Alzheimer's" and likely represent a variety of presentations but still well characterized by the TARCC inclusion criteria. To date, there is no absolute way of identifying "pure" AD cases while still alive and autopsy-confirmed case studies oftentimes limit the search to later stages in the disease course, which is less relevant to work looking at preventing or slowing the disease.

Other limitations include the reliance on informant report of BADLs. The validity of informant based assessment of activities of daily living has been questioned and more direct methods of assessment have been suggested [40]. Although this may be true for more complex IADLs that may not be directly observed, it is likely that assessment of the behaviors under study and determination of the level of assistance required were more observable and the caretaker evaluations more valid. Another limitation relates to the large number of analyses conducted increasing the likelihood of Type I error. The present study represents an exploratory investigation that lays the groundwork for further studies that can test the relationships found in our research. Lastly, while we investigated the link between a range of biomarkers that have been related to AD and functional status, it is likely that there are important markers that were not included in this study.

It could be argued that the findings of the current study are simply a reflection of a confounding between markers of basic activities of daily living and markers of AD status. However, since AD itself is an underlying pathway to functional impairment, you would expect some relationship but the nature and specificity of the relationships along with the gender differences suggests that we are identifying pathological pathways distinct from disease status. If we can separate out markers of disease presence from markers of poor outcome (e.g. functional impairments), we may be able to identify mechanisms that may lead to slowing affects on functional behaviors.

In conclusion our study has shown the relationship of a relatively limited number of biomarkers of inflammatory processes to the need for assistance in conducting basic activities of living even in the relatively early stages of AD. Therefore, if there were potentially markers that were specifically related to ADLs this may provide keys into intervention strategies aimed at slowing progression from MCI to AD. Future studies would need to expand the search for other biomarkers for ADLs among MCI and AD cohorts with the current findings as justification for such projects. Our study has shown distinct biomarker profiles for Males and Females and underscores the need to study gender effects directly in research on the relationship of biomarkers to functional behavior in AD. Finally, these findings are supportive of the role of inflammatory biomarkers in the decline of functional behavior.

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Table 1

Characteristics of the sample

	Total Sample N= 196	**Males N= 67**	**Females N= 129**	**p**
Age	77.41 (SD= 8.291)	75.71 (SD= 8.272)	78.37 (SD= 8.174)	.169
Education	13.98 (SD= 3.538)	14.24 (SD= 3.538)	13.85 (SD= 3.387)	.514
MMSE	19.18 (SD= 6.222)	19.29 (SD= 7.444)	19.12 (SD= 5.514)	.898
ADL Total Score	9.42 (SD= 4.261)	9.25 (SD= 4.517)	9.51 (SD= 4.137)	.768
APOE4 Status Carriers/Non-Carriers	82/114	27/40	55/74	.871

Table 2

Biomarkers included in analyses

Beta 2 microglobulin
BDNF
Complement 3
CRP
Eotaxin
Factor VII
Fas Ligand
Ferritin
Fibrinogen
IL 5
IL 7
IL 8
IL 10
IL12p40
IL 15
MMP3
Stem Cell Factor
Tenascin C
TNFα
TNFβ
TNF RII
von Willebrand Factor

Table 3

Regression of biomarkers and BADLs for total sample N=196

Function	Biomarkers	Beta	SE	p	R^2	Adjusted R^2
BADL Total	IL7 Tenascin C IL12p40 Complement 3 Beta 2 microglobulin	-1.538 1.853 .696 2.813 .971	.250 .225 .281 .567 .349	.000 .000 .014 .000 .006	.376	.359 F= 22.889 5, 190 P= .000
Toileting	IL7 Tenascin C Beta 2 microglobulin Complement 3	-.307 .459 .403 .686	.061 .065 .076 .166	.000 .000 .000 .000	.307	.292 F= 21.112 4, 191 p= .000
Feeding	IL7 Tenascin C Fibrinogen	-.178 .138 .060	.032 .032 .020	.000 .000 .003	.214	.202 F= 17.472 3, 192 p= .000
Feeding	IL7 Tenascin C Fibrinogen	-.178 .138 .060	.032 .032 .020 .003	.000 .000	.214	.202 F= 17.472 3, 192 p= .000
Dressing	IL7 Tenascin C IL12p40 Complement 3 IL15	-.294 .288 .255 .492 -.167	.064 .052 .058 .126 .063	.000 .000 .000 .000 .009	.339	.322 F= 19.515 3, 192 p= .000
Grooming	IL7 IL12p40 Tenascin C Complement 3 CRP IL8	-.287 .186 .330 .489 .071 -.187	.054 .053 .059 .144 .035 .084	.000 .001 .001 .001 .042 .027	.282	.259 F= 12.377 6, 189 p= .000
Ambulation	Beta 2 microglobulin Tenascin C Complement 3 CRP	.307 .243 .303 .050	.057 .059 .117 .033	.000 .000 .015 .015	.205	.189 F= 12.333 4, 191 p= .000
Bathing	IL7 Tenascin C IL12p40 Complement 3	-.307 .292 .206 .507	.053 .050 .040 .129	.000 .000 .000 .000	.241	.225 F= 15.167 4, 191 p= .000

Table 4

Regression of biomarkers and BADLs for males (N=67)

Function	Biomarkers	Beta	SE	p	R^2	Adjusted R^2
BADL Total	IL15 IL12p40 Complement 3 Stem Cell Factor	-2.111 1.503 3.764 1.030	.340 .381 1.529 .495	.000 .000 .017 .042	.459	.424 F= 13.140 4, 62 p= .000
Toileting	IL15 TNF RII Complement 3 IL5	−.253 .586 1.096 −.213	.092 .145 .374 .089	.008 .000 .005 .019	.418	.380 F=11.121 4, 62 p= .000
Feeding	IL15 Fibrinogen MMP3 Complement 3	−.223 .160 .135 .517	.045 .040 .060 .240	.000 .001 .029 .035	.379	.339 F= 9.476 4, 62 p= .000
Dressing	IL15 IL12p40 Stem Cell	−.566 .367 .259	.080 .092 .119 .033	.000 .000	.450	.424 F= 17.172 3, 63 p= .000
Grooming	IL15 Complement 3 von Willebrand Factor	−.318 .956 .246	.065 .334 .092	.000 .006 .010	.374	.345 F= 12.565 3, 62 p= .000
Ambulation	TNF RII Eotaxin	.460 .311	.127 .098	.000 .002	.197	.172 F= 7.831 2,64 p= .000
Bathing	IL15 Complement 3 IL12p40	−.343 .845 .172	.079 . 361 .024	.000 022 .023	.315	.283 F= 10.552 5, 53 p= .000

Table 5

Regression of biomarkers and BADLs for females (N= 129)

Function	Biomarkers	Beta	SE	p	R^2	Adjusted R^2
BADL Total	IL7	−2.010	.344	.000	.469	.438 F= 15.264 7, 121 p= .000
	Tenascin C	2.368	.306	.000		
	IL15	.805	.337	.019		
	CRP	.294	.167	.081		
	Complement 3	2.630	.676	.000		
	IL12p40	.705	.294	.018		
	IL8	−1.165	.449	.011		
Toileting	IL7	−.375	.091	.000	.253	.235 F= 14.106 3, 125 p= .000
	Tenascin C	.388	.078	.000		
	TNR RII	.441	.150	.004		
Feeding	IL7	−.241	.050	.000	.274	.251 F= 11.704 4, 124 p= .000
	Tenascin C	.193	.038	.000		
	TNF RII	.173	.020	.014		
	IL15	.131	.053	.015		
Dressing	IL7	−.333	.067	.000	.379	.354 F= 15.033 5, 123 p= .000
	Tenascin C	.434	.064	.000		
	IL12p40	.150	.063	.020		
	Complement 3	.617	.140	.000		
	IL8	−.237	.099	.019		
Grooming	IL7	−.382	.067	.000	.363	.331 F= 11.566 6, 122 p= .000
	Tenascin C	.310	.059	.000		
	CRP	.102	.037	.007		
	IL12p40	.321	.089	.000		
	Factor VII	−.176	.072	.016		
	Ferritin	.124	.059	.037		
Ambulation	CRP	.087	.037	.021	.230	.205 F= 9.261 4, 124 p= .000
	Beta 2 Microglobulin	.208	.064	.001		
	Tenascin C	.261	.061	.000		
	Fibrinogen	.081	.039	.041		
Bathing	Tenascin C	.397	.064	.000	.297	.275 F= 13.109 4, 124 p= .000
	Fibrinogen	.117	.043	.008		
	IL7	-.326	.081	.000		
	IL15	.256	.084	.003		

Table 6

Significant biomarkers by gender

Males	**Females**
IL 15	***IL 15***
IL 12p40	***IL 12p40***
Complement 3	***Complement 3***
TNF RII	***TNF RII***
Fibrinogen	***Fibrinogen***
Eotaxin 1	IL 7
IL 5	Tenascin C
MMP3	IL 8
Stem Cell Factor	Beta 2 Microglobulin
von Willebrand Factor	CRP
	Factor VII
	Ferritin

Biomarkers appearing in significant regression equations for both Males and Females are in bold.