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Molecular markers of neuropsychological functioning and Alzheimer's disease

Melissa Edwards[a], Valerie Hobson Balldin[b], James Hall[c,d], Sid O'Bryant[d,e,*]

[a]Department of Psychology, University of North Texas, Denton, TX, USA
[b]Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[c]Department of Psychiatry, University of North Texas Health Science Center, Fort Worth, TX, USA
[d]Institute for Aging & Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, TX, USA
[e]Department of Internal Medicine, University of North Texas Health Science Center, Fort Worth, TX, USA

Abstract

Background: The current project sought to examine molecular markers of neuropsychological functioning among elders with and without Alzheimer's disease (AD) and determine the predictive ability of combined molecular markers and select neuropsychological tests in detecting disease presence.
Methods: Data were analyzed from 300 participants (n = 150, AD and n = 150, controls) enrolled in the Texas Alzheimer's Research and Care Consortium. Linear regression models were created to examine the link between the top five molecular markers from our AD blood profile and neuropsychological test scores. Logistical regressions were used to predict AD presence using serum biomarkers in combination with select neuropsychological measures.
Results: Using the neuropsychological test with the least amount of variance overlap with the molecular markers, the combined neuropsychological test and molecular markers was highly accurate in detecting AD presence.
Conclusion: This work provides the foundation for the generation of a point-of-care device that can be used to screen for AD.

Keywords: Alzheimer's disease; Diagnosis; Biomarkers; Verbal fluency

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and is estimated to cost the U.S. healthcare system nearly $1.1 trillion dollars by the year 2050 [1]. Because of the growing prevalence rate of AD and the increase in preventative healthcare measures, which enable individuals to live longer, it is believed that over 80% of those 65 years and more will experience cognitive decline associated with AD [1]. Thus the importance of identifying early AD symptoms has increased as the burden on the healthcare system continues to grow. Recent work has sought to establish a rapid and cost-effective means of identifying those with early AD, through creating a blood test to screen for disease presence [2–6].

Through this work, researchers have sought to provide utility for identifying blood-based biomarkers associated with neuropsychological functioning to establish biomarker profiles of disease states [7]. This effort termed Molecular Neuropsychology has identified biomarker profiles of neurocognitive functioning and begun combining select blood biomarkers with select cognitive assessments with the goal of establishing a point-of-care device for primary care settings that can be used to identify those with early AD [7,8]. This work has stemmed from the growing need for a rapid screening measure for those early in the disease process. These methods can also be used for screening in clinical trials.

Initial work by Ray and colleagues established an 18-plasma-based blood test to differentiate those with AD from those with normal cognition, with an overall accuracy of 89% [9]. This work was built on by O'Bryant and colleagues [2–4] who examined the implications of using

*Corresponding author. Tel.: 817-735-2961; Fax: 817-735-0628.
E-mail address: Sid.obryant@unthsc.edu

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serum-based biomarkers to create an algorithm to detect AD presence. In our most recent work, we generated a blood test based profile consisting of 21 serum proteins, which yielded an accuracy of 96% in identifying those with AD from those with normal cognition [4]. The top five serum proteins included in the blood-test were interleukin 5 (IL-5), IL-6, IL-7, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [4].

In our recent work, we demonstrated that combining two of the top five biomarkers (TNF-α and IL-7) with one neuropsychological measure (Clock 4-point), yielded excellent accuracy in detecting early AD [8]. Even for very early AD cases, this approach was able to provide an overall accuracy of 91% with a sensitivity of 97% and specificity of 72% [8]. This work has shown that combining neuropsychological screening measures with a limited number of biomarkers can increase the ability to identify those who are at a higher risk for the development of AD.

AD pathology has become increasingly linked with inflammation, specifically among Non-Hispanic whites [4,10,11]. IL-5, -6, and -7 were found to be some of the top serum-based proteins among individuals with AD [4]. Although inflammatory blood-based biomarkers have been established as predictors of AD presence, outside our laboratory, few studies to date have sought to examine how much variance is accounted for by the biomarkers themselves in relation to measures of cognition [7]. Given that these biomarkers are associated with AD, it is hypothesized that the markers will account for a significant amount of variance in memory scores. This project sought to examine molecular markers of neuropsychological functioning among elders with and without AD and sought to determine the predictive ability of combined molecular markers and select neuropsychological tests in detecting disease presence.

2. Methods

2.1. Participants

Data were analyzed from 300 participants (n = 150, AD and n = 150, normal cognition) enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC). The TARCC protocol has been well documented elsewhere [12,13]. Briefly, the methodology for the TARCC study includes having each participant undergo an annual standardized assessment at one of the six participating sites, which includes a medical evaluation, neuropsychological evaluation, a clinical interview, and a blood draw. The diagnosis of AD is based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [14] and healthy controls performed within normal limits on neuropsychological testing. All participants also had a Clinical Dementia Rating (CDR) assigned. Institutional Review Board approval was obtained at each site and written and informed consent was obtained.

2.2. Human serum sample collection

Nonfasting blood samples were collected in 10 ml of tiger-top tubes. The obtained serum samples were allowed to clot in a vertical position for approximately 30 minutes at room temperature. The samples are then centrifuged for 10 minutes at the speed of 1300 ×g within 1 hour of collection. Then 1.0 ml of aliquots of serum are transferred into cryovial tubes with Freezerworks™ barcode labels firmly affixed to each aliquot. Samples are then placed in −80°C freezer within 2 hours of collection for storage until use in an assay. Serum was assayed in duplicate via a multiplex biomarker assay platform using electrochemiluminescence (ECL) on the SECTOR Imager 2400A from Meso Scale Discovery (MSD; http://www.mesoscale.com). The MSD platform has been used extensively to assay biomarkers of AD [15,16]. ECL measures are considered to be more conventional than those of enzyme-linked immunosorbent assay, which are the current standard for most assays because of their increased sensitivity [15].

2.3. Neuropsychological testing

The core neuropsychology battery for the TARCC includes commonly used instruments for detection of AD in both clinical and in research settings. The battery includes the following tests: Trail-Making Test [17], Boston Naming Test (30- and 60-items versions) [18], verbal fluency (Controlled Oral Word Association Task [COWAT], Animals) [18], Clock-Drawing Test (4-points) [18], American National Adult Reading Test [18], digit span (Wechsler Adult Intelligence Scale-Revised, Wechsler Adult Intelligence Scale Third Edition, Wechsler Memory Scale-Revised [WMS-R]) [19], WMS Logical Memory and Visual Reproduction (WMS-R and WMS-III) [19], the Geriatric Depression Scale (GDS-30) [20], the Mini-Mental State Examination [21], and ratings on the CDR [22]. Scores were equated across versions by using scale scores as outcome variables in analyses.

2.4. Statistical analyses

Linear regression models were created to examine the link between the top five molecular markers from our AD blood profile [4] (IL-5, IL-6, IL-7, TNF-α, CRP) and neuropsychological test scores. Next, logistical regressions were used to predict AD presence using the serum biomarkers in combination with the select neuropsychological measures that were least related to the biomarker profile.

3. Results

Demographic characteristics of the TARCC samples are presented in Table 1. AD cases were found to be older ($P < .001$), have fewer years of education ($P = .003$) and be predominantly female ($P < .001$). Significant differences were also observed across the molecular markers used. Those with AD, were found to have higher levels of IL-7 ($P < .001$), TNF-α ($P < .001$), and IL-6 ($P < .001$) as

Table 1
Demographic characteristics

	Alzheimer's disease mean (SD)		Normal control mean (SD)	
	Mean (SD)	Range	Mean (SD)	Range
Gender, male	30%		32%	
Age	76.1 (8.6)	54–105	71.2 (9.2)	50–94
Education	14.7 (3.0)	0–23	15.5 (2.6)	0–23
Race/ethnicity				
Hispanic Mexican American	3%		7%	
Non-Hispanic white	96%		90%	
CDR-SB	7.8 (4.1)	0–18	0.0 (0.1)	0–3
MMSE	19.1 (6.3)	0–30	29.1 (1.4)	18–30
COWAT scaled score	7.2 (3.4)	2–18	10.9 (3.1)	2–18
CRP (μg/L)	3.0 (4.4)	0–25.0	4.1 (4.2)	0.1–25.0
IL-5 (μg/L)	3.1 (19.6)	0.4–32.0	3.8 (18.7)	0.4–26.0
IL-6 (μg/L)	5.0 (5.5)	0.7–43.0	2.1 (2.2)	0.2–13.0
IL-7 (μg/L)	10.4 (4.4)	6.5–376.0	5.0 (2.5)	6.5–263.0
TNF-α (μg/L)	3.4 (3.6)	1–64	1.3 (0.8)	1–93

Abbreviations: SD, standard deviation; CDR-SB, Clinical Dementia Rating; MMSE, Mini-Mental State Health Examination; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor.

compared with normal cognitive control cases. Group differences were also identified wherein lower levels were found among AD cases in CRP ($P = .001$) levels and there was also a trend toward significance related to lower IL-5 ($P = .05$) levels.

The combined molecular markers were significantly related to cognitive test scores and accounted for a significant amount of variance: COWAT (B[SE] = −0.62[0.12], $P < .001$, 5%), Logical Memory I (B[SE] = −15.59 [502.18], $P = .97$, 19%), Logical Memory II (B [SE] = −9.18[554.95], $P = .98$, 20%), Visual Reproduction I (B[SE] = −1.37[0.34], $P < .001$, 19%), Visual Reproduction II (B[SE] = −47.16[599.87], $P = .93$, 22%), trail making test A (B[SE] = −0.49[0.10], $P < .001$, 8%), trail making test B (B[SE] = −0.57[0.10], $P < .001$, 13%), and Boston naming test 60-item (B[SE] = −0.54[0.10], $P < .001$, 14%). The COWAT was found to have the least amount of variance overlap with the molecular markers and was selected for combination with the markers for predicting AD presence. This was done to maximize the strengths of the approach by minimizing overlap. The COWAT requires participants to generate words that begin with a specific letter of the alphabet within a predetermined time frame [18]. The COWAT is designed to test for verbal fluency, specifically, phonemic fluency. In prior work, the COWAT has been shown to distinguish mildly impaired AD cases from normal controls due to its requirement of concurrent manipulation of information (set formation and set shifting) [23].

When examining the predictive ability of the biomarker-cognitive profile in detecting AD (Table 2), the combination of demographic variables + five molecular markers alone were relatively accurate in detecting disease presence (Area Under the Curve [AUC] = 0.87). Lower accuracy was detected when combining only demographic factors + one neuropsychological test (COWAT) (AUC = 0.77). Comparatively, the combination of demographics + one neuropsychological test (COWAT) + five molecular markers were found to be highly accurate in detecting AD presence (sensitivity and specificity of 90% and 92%, respectively) with an overall accuracy of 91%.

4. Conclusions

A combination of blood-based biomarkers + cognitive measure + demographics has yielded excellent diagnostic accuracy in detecting the presence of AD even in early stages [8]. The current project sought to further refine prior research by examining the strength of the relationship of the top five molecular markers from our recently published AD algorithm [4] with neuropsychological test scores. The molecular markers accounted for a significant amount of variance in neuropsychological test scores, specifically with measures related to memory. This finding is not surprising given that the blood-based biomarker algorithm is highly accurate in detecting AD where memory deficits are the core cognitive feature. Among the neuropsychological measures, the COWAT a measure of phonemic fluency had the least amount of shared variance with the molecular markers. Combining five molecular markers with this single neuropsychological test yielded an excellent overall accuracy of 91%.

Table 2
Analysis of biomarker-cognitive profile to detect Alzheimer's disease

	Sensitivity (SN)	Specificity (SP)	Overall accuracy
Demographics + COWAT	0.76	0.77	0.77
Demographics + IL-5, IL-6, IL-7, CRP, TNF-α	0.87	0.88	0.87
Demographics + IL-5, IL-6, IL-7, CRP, TNF-α + COWAT	0.90	0.92	0.91

Abbreviations: COWAT, Controlled Oral Word Association Task; IL, interleukin; CRP, C-reactive protein; TNF-α, tumor necrosis factor.

Prior work with the same blood based biomarkers has supported their link with the domains of language, executive functioning, and memory [3]. There is extensive literature to support the association between verbal fluency deficits and AD with several studies indicating that changes in verbal fluency can begin up to five years before diagnosis [24,25]. Additional studies have shown a pronounced decrease in the ability to generate words among those with AD pathology [26–30]. Impaired phonemic fluency has been linked to greater executive dysfunction and may provide a better assessment of the frontal regions of the brain when compared with semantic network tasks [31]. Moreover, some studies suggest that phonemic fluency is only mildly impaired among AD cases compared with other measures of verbal fluency [29,32–34]. Therefore, subtle changes in phonemic fluency may represent underlying pathological changes, which are sensitive to changes in disease state.

With regards to the molecular marker change in CRP levels observed between diagnostic groups, our findings are consistent with prior work from our group and others who have previously found CRP levels to be decreased among non-Hispanic white AD cases as compared with cognitively normal controls [35–37]. However, we have also found increased CRP levels to be related to poorer outcomes among Hispanics, findings which have been replicated by others [37,38]. There is consistent evidence to suggest that inflammatory processes, marked by fluctuations in markers such as CRP or IL-5, are linked with risk for late life AD [2–4,35–38]. Work related to inflammatory processes among our group has led to the proposed existence of a proinflammatory endophenotype, which can explain noted molecular marker changes with increased disease severity [2–4]. Additional work will seek to address the proposed endophenotype along with changes this may pose to the molecular marker + cognitive measure profile for disease presence particularly across ethnicities.

There are several limitations with this study that impact the generalizability of the findings. One limitation is the demographics of the sample, which is comprised predominately of white, well-educated, females. Additionally, the TARCC battery is heavily weighted toward measures of memory and further research using other measures of executive functioning may enhance the utility of the approach. It is also possible that stage of disease is differentially impacted by the selected molecular markers, which implicates that a different measure of cognitive functioning could be more reliable in detecting the presence of AD at earlier stages. Follow-up work is being conducted to examine this potential to establish relative changes in molecular markers + cognitive measures in detecting disease presence/severity from subjective memory complaints and mild cognitive impairment stages to AD.

Use of a point-of-care device, which incorporates molecular markers with cognitive measures, has significant utility in clinical settings particularly within primary care. As physicians have a limited amount of time with patients, a time-and cost-effective measure to identify those who would benefit from follow-up assessments at a specialty care clinic has the potential to increase early diagnostics and provide necessary care early on, when it is most effective. Additionally, a point-of-care device has the opportunity to serve as a means of screening into clinical trials and aid in the differential diagnoses as several neurodegenerative diseases present with similar symptoms at onset. Moreover, minority populations often present earlier with cognitive impairment and frequently go undiagnosed until later stages in the disease. A point-of-care device could help serve this population and increase access to care and appropriate treatment referrals.

Combining a measure of verbal fluency that reflects executive functioning with biomarkers that are more strongly related to memory processes produces a highly accurate tool to detect Alzheimer's disease. This work provides the foundation for the generation of a point-of-care device that can be used to screen for AD with screen positives referred for a comprehensive dementia examinations, including amyloid beta positron emission tomography scans, cerebrospinal fluid, and/or clinical evaluations. Further research focusing on the use of this combination in individuals with subjective cognitive complaints or mild cognitive impairment, may allow increased ability to predict cognitive decline or conversion to Alzheimer's. Our work is the first to combine molecular markers with measures of cognition in an effort to identify AD. More research is needed to examine the broader implications of combining molecular markers with cognitive measures for purposes of enhancing diagnostics.

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Knebl, DO, Robert C. Barber, PhD, Douglas Mains, Lisa Alvarez, Erin Braddock, Rosemary McCallum; University of Texas Southwestern Medical Center: Perrie Adams, PhD, Roger Rosenberg, MD, Myron Weiner, MD, Mary Quiceno, MD, Benjamin Williams, MD, Ryan Huebinger, PhD, Guanghua Xiao, PhD, Doris Svetlik, Amy Werry, Janet Smith; University of Texas Health Science Center–San Antonio: Donald Royall, MD, Raymond Palmer, PhD, and Marsha Polk.

RESEARCH IN CONTEXT

1. Systematic review: A literature review was conducted to evaluate the current state of work examining the use of blood-based biomarkers in the detection of Alzheimer's disease (AD). Prior research looking at the utility of implementing molecular markers with cognitive measures for purposes of screening for AD presence was also reviewed.
2. Interpretation: Molecular markers were found to differentially relate to specific cognitive measures, with the measure of verbal fluency showing the least amount of variance. When select molecular markers were combined with one measure of fluency and demographics it was highly accurate in the detection of AD.
3. Future directions: This work seeks to establish a point-of-care device that can be used for diagnostic and prognostic purposes for AD. Further work should focus on this combination of molecular markers and cognitive measures among individuals with subjective cognitive complaints or mild cognitive impairment.

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