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Combining Select Neuropsychological Assessment With Blood-Based Biomarkers to detect Mild Alzheimer's disease: A Molecular Neuropsychology approach

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Abstract

Background—The current project sought to create combined biomarker-cognitive profile to detect mild Alzheimer's disease.

Methods—Data was analyzed from 266 participants (129 AD cases [Early AD n=93; Very Early AD n=36]; 137 controls) enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC). Non-fasting serum samples were collected from each participant and assayed via a multi-plex biomarker assay platform using electrochmiluminescence (ECL). Logistic Regression was utilized to detect early AD using two serum biomarkers (TNFα and IL7), demographic information (age) and one neuropsychological measure (Clock-4 point) as predictor variable. Disease severity was determined via Clinical Dementia Rating scale global scores.

Results—In the total sample (all levels of CDR scores), the combination of biomarkers, cognitive test score, and demographics yielded the obtained sensitivity (SN) of 0.94, specificity (SP) of 0.90 and an overall accuracy of 0.92. When examining early AD cases (i.e. CDR=0.5-1), the biomarker-cognitive profile yielded SN of 0.94, SP of 0.85 and an overall accuracy of 0.91. When restricted to very early AD cases (i.e CDR=0.5), the biomarker-cognitive profile yielded SN of 0.97, SP of 0.72 with an overall accuracy of 0.91.

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Conflict of Interest

None to disclose.

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Conclusions—The combination of demographics + 2 biomarkers + 1 cognitive test created a biomarker-cognitive profile that was highly accurate in detecting AD presence, even in the very early stages. This work demonstrates the complementary nature of each modality (blood biomarkers + neuropsychological assessment) and supports our previously proposed concept for Molecular Neuropsychology.

Keywords

Neuropsychology; Biomarkers; Alzheimer's Disease; Molecular

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and is estimated to impact over 5 million Americans [1]. AD is considered to be an age-associated disease with 80% of those 65 and above experiencing symptoms of cognitive decline [1]. Alzheimer's disease therefore poses a significant financial burden on the United States healthcare system with the current estimated annual cost of $200 billion dollars with the cost estimated to reach $1.1 trillion dollars by 2050 [1]. Due to the growing prevalence rates, continuous research has focused on establishing accurate measures that will enable early detection of AD. The use of amyloid imaging and CSF based biomarkers has been recommended as valuable tools in early detection [2, 3]. These approaches have drawbacks related to cost or being invasive. Recent work has sought to utilize blood-based biomarkers as a means of providing a rapid and cost-effective method for the first-step in screening for disease presence.

Ray and colleagues identified an algorithm created from 18 plasma-based proteins, which was able to distinguish AD from healthy controls with an overall accuracy of 89% [4]. This work was able to discriminate MCI from cognitive normal controls with 81% accuracy [4]. These findings provided initial support for the use of blood-based biomarkers as an accurate and efficient screening tool for AD. More recent work by O'Bryant and colleagues has sought to improve the accuracy of blood-based biomarkers in identifying AD. Their work generated an algorithm based on 30 serum-based proteins, which yielded an accuracy level of 88% in identifying AD cases from healthy controls [5]. When demographic variables were entered into the algorithm, in addition to the 30 serum-based proteins, the overall accuracy level increased to 94% [5]. This algorithm was later refined to 8 serum-based proteins, which yielded an overall accuracy of 98% in discriminating AD cases from healthy controls [6]. The top two serum-based biomarkers for the AD profile included tumor necrosis factor-alpha (TNFα) and interleukin 7(IL7) [7].

The pathology of AD has been increasingly linked with mechanisms related to inflammation [8, 9]. TNFα is an inflammatory cytokine that is considered to be strongly associated with the neuropathology of AD through serving as a mediator of synaptic dysfunction [10]; and higher levels of TNFα have been found in the CSF of individuals with AD [11]. There have been conflicting findings on TNFα levels in serum samples of those with AD with some studies indicating a decrease in TNFα levels in AD patients when compared to healthy controls [12, 13] while others find no difference between groups [11]. Another pro-inflammatory biomarker, IL7, which is involved in the development and differentiation of

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both T cells and B cells, has been linked to AD [14]. Specifically, IL7 accounted for more variance in those with AD across several studies that sought to identity biomarkers of cognitive dysfunction [5, 7, 15].

The use of a Clock Drawing Test (CDT) has long been supported as a rapid and cost-effective means of screening for dementia, specifically AD [16 – 20]. The ability of the CDT to test language comprehension, memory, visuospatial, and executive functioning enables it to identify those cognitive domains which are more likely to be impaired early in the AD process [21]. However, its use as a screen for those with early to very early Alzheimer's disease has been varied [21] with empirical support implicating that the CDT is not sensitive enough to detect early progression. To date, no study has looked at utilizing the CDT in combination with proteomics for purposes of increasing the overall accuracy of detecting those with early AD.

Prior work has sought to identify serum-based biomarker algorithms of specific neuropsychological functioning [7]. This work, termed Molecular Neuropsychology, provided an initial demonstration of the utility of algorithms combining blood-based biomarkers with neuropsychological functioning and also identified biomarker profiles associated with specific cognitive domains [7]. The ability to integrate biomarkers and cognitive screening tools can be utilized for the generation of an innovative point-of-care device for rapid and cost-effective screening within primary care settings. The current project sought to expand upon the work of O'Bryant and colleagues [7]. It was hypothesized that the combination of IL7, TNFα and CDT would be highly accurate in detecting early cases of Alzheimer's disease.

Materials and Methods

Participants

Data were analyzed from 266 participants (129 AD cases [Early AD n=93; Very Early AD n=36]; 137 controls) enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC). 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. Diagnosis of AD is based on NINCDS-ADRDA criteria [22] and those classified as healthy controls were those identified to have performed within normal limits on neuropsychological testing. All participants who met NINCDS-ADRDA criteria for AD had a Clinical Dementia Rating (CDR) assigned. Those with very early AD obtained a CDR score of 0.5, whereas those participants with a CDR score of 0.5-1.0 were classified as early AD. Institutional Review Board approval was obtained at each site and written and informed consent was obtained for all those who met criteria for participation in the TARCC study.

Human serum sample collection

Non-fasting blood samples were collected based on the outlined TARCC protocol. 10mL tiger-top tubes were used to collect the non-fasting serum blood samples. The obtained serum samples were allowed to clot in a vertical position for approximately 30 minutes at

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room temperature. The samples are then centrifuged for 10 minutes at the speed of 1300xg, aliquotted into 0.5mL tubes and stored at −80° until assay. The entire sample processing time (blood draw to freeze) was less than two hours. The non-fasting serum samples were then assayed via a multi-plex biomarker assay platform using electrochmiluminescence (ECL) on the SECTOR Imager 2400A from Meso Scale Discovery (MDS).

Neuropsychological Testing

The core neuropsychology battery for the TARCC includes commonly utilized instruments for detection of AD in both clinical as well as in research settings. The battery includes the following tests: Trail-Making Test [23], Boston Naming Test (30- and 60-items versions) [24], verbal fluency (FAS, Animals) [24], Clock-Drawing Test (4-points) [24], American National Adult Reading Test (AMNART) [24], digit span (WAIS-R, WAIS-III, or WMS-R) [25], WMS Logical Memory and Visual Reproduction (WMS-R or WMS-III) [25], the Geriatric Depression Scale (GDS-30) [26], the Mini-Mental State Examination (MMSE) [27], and ratings on the Clinical Dementia Rating Scale (CDR) [28].

The Clock-Drawing Test (4-points)[24] requires participants to draw a clock face and place the hands and numbers on the clock to read a predetermined time [24]. The CDT is designed to screen for dementia, as well as test for visuospatial and constructional abilities, and executive deficits. The CDT is both a reliable and valid measure of cognitive functioning, and has good psychometric properties and diagnostic accuracy [24].

Statistical Analyses

Logistic Regressions were utilized to detect early AD using two serum biomarkers (TNFα and IL7), demographic information (age, gender, and education) and one neuropsychological measure (Clock-4 point) as predictor variables. Disease severity was determined via Clinical Dementia Rating (CDR) scale global scores.

Results

Demographic characteristics of the TARCC samples were provided in Table 1. Those with AD were found to be older (mean[SD]=76[8.6]) and to have one less year of education (mean[SD]=14.7[3.0]) as compared to cognitively normal cases. When broken down by very early AD and early AD, very early AD cases were shown to be younger (mean[SD]=72.6[8.1]) as compared to early AD cases (mean[SD]=74=[8.6]). No differences were observed in level of education between very early AD and early AD cases as both groups had a mean of 13 years.

On neuropsychological testing, AD cases had lower Clock 4-point scores (mean[SD]=2.9[1.0]) as compared to cognitively normal cases (mean[SD]=3.7[0.5]). Furthermore, AD cases were also shown to have substantially higher CDR sum of boxes scores with a mean score of 7.8 as compared to those with normal cognition. When examining very early AD and early AD cases, very early AD cases had higher Clock-4 scores (mean[SD]=3.5[0.7]) as compared to early AD cases (mean[SD]=3.1[1.0]).

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Differences in biomarkers were also observed with AD cases having higher mean levels of IL7 and TNF alpha (83.4 μg/L and 10.3 μg/L) when compared to their cognitively normal counterparts (50.6 μg/L and 15.7 μg/L). When examining very early as compared to early AD cases, those in the very early AD stage had lower levels of IL7 with a mean of 47.7 μg/L as compared to early AD cases with a respective mean of 53.1 μg/L. No group differences were noted between TNF alpha levels between very early and early AD cases with respective means of 16.8 μg/L and 16.1 μg/L.

In the total sample (all levels of CDR scores), the combination of biomarkers, cognitive test score, and demographics yielded the obtained sensitivity (SN) of 0.94, specificity (SP) of 0.90 and an overall accuracy of 0.92. When examining early AD cases (i.e. CDR=0.5-1), the biomarker-cognitive profile yielded SN of 0.94, SP of 0.85 and an overall accuracy of 0.91. When restricted to very early AD cases (i.e CDR=0.5), the biomarker-cognitive profile yielded SN of 0.97, SP of 0.72 with an overall accuracy of 0.91.

Discussion

The combination of demographics + 2 biomarkers + 1 cognitive test created a biomarker-cognitive profile that was highly accurate in detecting AD presence, even in the very early stages. It is noteworthy that only two blood-based biomarkers were utilized. This is an important finding as if this line of work is to yield a point-of-care device; the proteomic component must be highly accurate though with few markers. Interestingly, while age, education and gender were significant predictors of disease state when only cognitive testing was utilized, once the biomarkers were entered into the model, age was the only demographic variable that continued to add to the predictive accuracy of the model. This work demonstrates the complementary nature of each modality (blood biomarkers + neuropsychological assessment) and further supports the concept for Molecular Neuropsychology. The current team is now working towards the identification and/or generation of a point-of-care method for select proteomic analyses.

Findings from this study suggest the utility of combining cognitive measures with proteomics, in increasing the ability of neuropsychological screening measures to accurately identify those who are at higher risk for AD and require more extensive evaluations. The derived biomarker-cognitive profile was created to serve as a screening tool within primary care settings. This method would serve well to identify those elders who should be referred for confirmatory diagnosis via clinical, neuroimaging and/or CSF analyses thereby increasing utility of these modalities.

The Clock Drawing Test is a quick and easy to administer neuropsychological test that is useful in screening for cognitive impairment. There is a possibility that other neuropsychological measures might add more to the biomarker-cognitive profile than the CDT even though the CDT is quick, easy to administer and efficient as a cognitive screen. Due to the documented limitations of CDT's ability to distinguish mild Alzheimer's disease cases, another well-established neuropsychological measure such as the controlled oral word association task may help to further refine the sensitivity and specificity of combining neuropsychological measures with biomarkers in identifying early cognitive impairment.

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The current team is investigating multiple cognitive measures to identify the ideal set of biomarker + cognitive measures for inclusion in the methods.

Limitations to the study include its limited sample size. Due to the distinction of very early from early AD cases, this resulted in a split of the AD sample thereby decreasing the sample size. An additional limitation of the group is the limited variability of the sample, which presents as predominantly Non-Hispanic White, higher educated and with an overall mean age of 74. A further limitation is the recruitment bias of the sample, which consisted of clinic samples from across the five TARCC sites. Therefore, the sample utilized may not adequately reflect the general population, however, recruitment from clinic settings has been implicated as being beneficial for targeting Alzheimer's disease cases.

Future research should look towards refining the combination of blood-based biomarkers and select neuropsychological measures in order to better improve the accuracy of identifying cases of mild Alzheimer's disease as well as the detection of mild cognitive impairment (MCI), which the current team is actively pursuing. Additional work by this team includes collection of data in an independent cohort for purposes of cross validating the molecular neuropsychological approach. Furthermore, this work should be examined among other ethnicities such as Hispanic Mexican Americans, as they have been identified to be a subset of the population with an increased susceptibility to cognitive impairment at earlier ages when compared to Non-Hispanic Whites and therefore may develop mild Alzheimer's disease at earlier time points.

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Table 1

Demographic Characteristics

	AD Mean (SD) N= 129	Very Early AD Mean (SD) N=36	Early AD Mean (SD) N=93	Control Mean (SD) N= 137
Gender Male (%)	30%	39%	41%	32%
Age	76.1(8.6)	72.6(8.1)	74.2(8.6)	71.2(9.2)
Education	14.7(3.0)	13.6(3.5)	13.7(3.1)	15.5(2.6)
Race/Ethnicity (%)				
Hispanic	3%	29%	23%	7%
Non-Hispanic White	96%	72%	77%	90%
CDR-SB	7.8(4.1)	0.50(0.0)	1.0(0.0)	0.0(0.1)
Clock (4- point)	2.9(1.0)	3.5(0.7)	3.1(1.0)	3.7(0.5)
IL7 (μg/L)	83.4(71.9)	47.7(52.8)	53.1(57.6)	50.6(54.8)
TNFα (μg/L)	10.3(10.7)	16.8(13.4)	16.1(13.3)	15.7(13.4)

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Table 2

Analysis of Biomarker-Cognitive Profile to Detect Mild Alzheimer's Disease

	Sensitivity (SN)	Specificity (SP)	Overall Accuracy
Total Sample + Biomarkers + Cognitive test+ Demographics (N= 266)	0.94	0.90	0.92
Early AD (CDR=0.5-1.0) + Biomarkers + Cognitive tests + Demographics (N= 93)	0.94	0.85	0.91
Very Early AD (CDR = 0.5) + Biomarkers + Cognitive tests + Demographics (N=36)	0.97	0.72	0.91