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RESEARCH ARTICLE

Depression and Plasma Biomarkers of Alzheimer's Disease in a Diverse Community Cohort: The Impact of Ethnicity and Level of Depression

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ABSTRACT

Background: Depression is both a risk factor for and early symptom of Alzheimer's disease. Numerous studies have investigated the relationship between AT(N) biomarkers of AD and depression; however, the majority of these have utilized CSF in Non-Hispanic White populations.

Objective: To investigate the relationship between plasma total Tau, $A\beta_{40}$, $A\beta_{42}$, NFL and depression in Mexican-Americans and Non-Hispanic Whites.

Methods: The study was a cross-sectional comparison of 645 Mexican American and 644 Non-Hispanic White older adults in a community-based study of cognitive aging who had been categorized as having unimpaired cognition using a consensus based algorithmic approach. Plasma biomarkers were assayed using Simoa technology. The Geriatric Depression Scale assessed depression.

Results: Mexican Americans had significantly higher scores on the GDS. Non-Hispanic Whites had higher $A\beta_{40}$, and $A\beta_{42}$ and MAs had higher NFL and Tau. For Mexican Americans, linear regression analyses found NfL and $A\beta_{42}$ significant predictors of GDS scores whereas for the Non-Hispanic White group none of the biomarkers was significantly related to GDS total score or any of the subscale scores. Those scoring in the depressed range had significantly higher levels of $A\beta_{40}$, $A\beta_{42}$, and NFL. When analyzed by ethnicity the depressed Mexican Americans had significantly higher levels of $A\beta_{40}$, $A\beta_{42}$, and NFL than the non-depressed. No difference between the depression levels on any of the biomarkers was found for Non-Hispanic Whites.

Conclusions: Findings support the importance of evaluating the effect of ethnicity and level of depressive symptoms when assessing the relationship of AD biomarkers to depression. In cognitively unimpaired MAs depression is related to the Alzheimer's Disease biomarkers but this is not the case for Non-Hispanic Whites. Higher levels of these biomarkers among depressed cognitively unimpaired Mexican Americans may be an indicator of increased risk for cognitive impairment but not for Non-Hispanic Whites. Longitudinal research is needed to clarify the effect of ethnicity on the biomarker-depression relationship.

Key Words: Plasma Biomarkers, Alzheimer's, Depression, Ethnicity

INTRODUCTION

A history of depression[1] and late life depression[2] have been linked to the development of cognitive decline and Alzheimer's disease[3]. Depression has been seen as both a risk factor for[4] and a prodromal symptom of Alzheimer's.[5] A number of studies have investigated the relationship between depressive symptoms and biomarkers of cognitive decline such as BDNF and markers of inflammation.[6-10] Consistent with the AT(N) framework[11] for Alzheimer's, researchers have looked at the relationship between markers of amyloid, tau and neurodegeneration and depressive symptoms.

Pomara et al.[12] found lower levels of CSF $A\beta_{42}$ in cognitively intact elderly NHWS with major depression. In a study of elderly women[13], it was found that those with depression had higher levels of CSF $A\beta_{42}$ than those without depression. A follow up study looking at additional CSF biomarkers found the depressed individuals had higher levels of $A\beta_{42}$ and NFL.[14] Johansson et al.[15] in a study of cognitively unimpaired older Swedes; found that CSF amyloid-β pathology predicted levels of apathy longitudinally.

Lower CSF levels of Aβ have been related to subsyndromal symptoms of depression in MCI.[16] Subsyndromal depression has been found to interact with high amyloid load to produce higher risk of cognitive decline and brain atrophy.[17] Higher levels of plasma total tau in cognitively normal elderly have been related neurobehavioral symptoms of Alzheimer's disease.[18] Tau but not amyloid biomarkers was found to be related to diagnosis of depression in older cognitively normal adults.[19] Yamazaki et al.[20] found plasma $A\beta_{40}$ predicted poor prognosis for depressed individuals with MCI. In a study of the trajectory of depression and apathy over time in prodromal Alzheimer's, lower $A\beta_{42}$ and higher tau were related to an increased likelihood of depression and apathy.[21]

Banning et al.[22] in a meta-analysis of studies on the relationship of biomarkers of Alzheimer's disease (amyloid, p-tau and markers of neurodegeneration) to affective symptoms including depression concluded that there were inconsistent findings likely related to differences in study design and the heterogeneity of affective symptoms. The majority of these studies looked at CSF markers rather than blood based markers and used a variety of measures of depression including the Geriatric Depression Scale (GDS). Few minority participants from the US were included in these studies and the impact of ethnicity has seldom been considered.

Latinos are the fastest growing minority in the US and Mexican Americans (MA) make up over 62% of this population.[23,24] MAs have a higher rate of Alzheimer's disease than non-Hispanic Whites (NHW)[25] and by 2050, the number developing some form of neurodegenerative disorders is predicted to increase six-fold. MAs also have a high rate of depression with a recent CDC study indicating over 28% of Latinos experience depression.[26] Given these rates of occurrence and the relative lack of research on plasma biomarkers in minority populations[27,28], the current study sought to investigate the depressive symptom-AD biomarker relationship in cognitively unimpaired MAs and NHWs.

MATERIALS and METHODS

Participants

Participants were from Health and Aging Brain Study- Health Disparities (HABS-HD) study, which is an ongoing community-based, multi-ethnic study regarding factors contributing to cognitive aging among Hispanic MAs as compared to NHWs. Data from 1289 participants (Mexican Americans N= 645 - Males= 258, Females= 387; Non-Hispanic Whites N=644 Males= 270, Females = 374) made up the sample. A full description of the HABS-HD protocol has been published elsewhere.[29] Briefly, the study protocol includes a functional exam, clinical labs, interview (medical history, family medical history and sociocultural factors), neuropsychological testing including the Geriatric Depression Scale to assess symptoms of depression, blood draw, and neuroimaging. Study material is administered in either English or Spanish per the participants reported language preference. The study protocol is conducted under IRB approved protocols and all participants and/or caregivers sign written informed consent. All participants are evaluated at a single site within the Institute of Translational Research at the University of North Texas Health Science Center, Fort Worth, Texas. All HABS-HD data is available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website.[30]

Geriatric Depression Scale

Depressive symptomology was assessed using the Geriatric Depression Scale[31] 30-item (GDS), a scale designed to be used for screening depression in the elderly. A factor analytic study[32] revealed four factors and based on that analysis, the GDS was divided into four symptom subscales. Dysphoria (11 items) – related to sad mood; Meaninglessness (7 items) – evaluating the meaning

or lack of meaning in one's life; Apathy (6 items) – associated with absence of motivation and Cognitive Impairment (6 items) – having awareness and concern of one's cognitive decline.

Diagnostic Classification

An automated decision tree has been implemented within the electronic data capture (EDC) system to determine and assign cognitive diagnoses. All files assigned with a diagnosis of cognitive impairment (MCI or dementia) undergo consensus review along with a random subset of 10% of files assigned as normal cognition. Unimpaired cognition is assigned based on the following: (1) no complaints of cognitive change (self or other), Clinical Dementia Rating[33] scale sum of boxes score = 0, cognitive test scores considered broadly within normal testing limits. Of note, if a participant has an isolated poor performance on neuropsychological testing, in the absence of any complaints, they are assigned as normal cognition.

APOE status was based on genotyping using commercially available TaqMan Genotyping Kits for rs429158 and rs7412 using the TaqMan GTXpress Master Mix (Thermo Fisher). Target amplification and detection was performed using the 7500 Real-Time PCR System (Applied Biosystems). APOE genotypes frequencies were confirmed to be in the Hardy-Weinberg equilibrium. Individuals classified as ε4/ε4 were considered APOE ε4 present and all others were considered APOE ε4 absent.

Assays

Blood Collection & Processing Procedures

Fasting blood collection and processing were completed based on the international guidelines for AD biomarker studies[34] and processed within 2 hours (stick-to-freezer). Samples were assayed in the University of North Texas Health Science Center Institute for Translational Research (ITR) Laboratory by the ITR Biomarker Core. The ITR Biomarker Core utilizes the Hamilton Robotics EasyBlood for blood processing, aliquoting and re-aliquoting. A custom Hamilton Robotics StarPlus system was utilized for preparation of all plates. Proteomic assays were run on a multi-plex biomarker assay platform using electrochemiluminescence (ECL) per our previously published methods using commercially available kits from Meso Scale Discovery (MSD) and Quanterix.

Samples

A total of 500µl of plasma was used to measure biomarker levels using the Single Molecule Array (Simoa) technology (Simoa; Quanterix, Lexington, MA, USA). Tests were performed to optimize dilution factors and centrifugation and the suggested dilution factor of 4x was used for the samples. After thawing, the samples were vortexed and spun at 10,000g for 5 minutes; the supernatant was directly transferred to a 96 well plate. The Coefficient of Variability (CV) for NFL was 0.038 and Lower Limit of Detection (LLOD) was reported at 0.038pg/mL.

Multiplexed detection of $A\beta_{42}$, $A\beta_{40}$ and Total Tau utilized Simoa technology. LLODs for $A\beta_{42}$, $A\beta_{40}$ and Total Tau were reported at 0.045pg/mL, 0.196pg/mL, 0.019pg/mL, respectively. Interplate CVs were derived for high and low pooled controls from the Quanterix automated system: $A\beta_{40}$ (High control CV=0.050, Low control CV= 0.042); $A\beta_{42}$ (High control CV= 0.051, Low control CV=0.040); Total Tau (High control CV=0.040, Low control CV= 0.047; NFL (high control CV= 0.035, Low control CV= 0.092).

Statistical Analyses

Data were analyzed using SPSS-25 (IBM). Independent t-tests were conducted to examine differences in demographic characteristics of age and education. Chi squared was applied to examine categorical data. ANOVA co-varying age, sex, education and APOEε4 status was used to assess group differences on GDS variables and biomarker levels and level of depression. Regression models were created to examine the link between the blood-based biomarkers of $A\beta_{40}$, $A\beta_{42}$, total Tau, NFL and symptoms of depression for each group separately. Statistical significance was set at $p<0.05$.

RESULTS

The characteristics of the sample are presented in Table 1. Overall, MAs were significantly younger and had significantly fewer years of education than NHWs. The distribution of the sexes was significantly different with the MA sample composed of a significantly higher percentage of females. NHWs had a significantly higher percentage of participants who had APOEε4present. Although MA females scored higher than the MA males on the GDS, the difference did not reach significance (Females M= 6.336, SD= 6.257; Males M= 5.353, SD= 5.610, t= 1.912 p= .056). There was not a significant difference between the sexes on the number of depressive symptoms endorsed for the NHW sample (Females M= 4.405, SD= 4.963; Males M= 4.000, SD= 4.432 t= 0.124 p= .902). As a group, MAs endorsed significantly more symptoms of

depression. On the subscales, MAs endorsed significantly more symptoms of Dysphoria and Cognitive Impairment. MAs and NHWs did not differ on the number of symptoms of Meaninglessness and Apathy reported.

Table 1. Characteristics of the Sample

	Mexican Americans N-=645	Non-Hispanic Whites N= 644	
Age	M= 63.2827 SD= 7.7084	M= 68.9015 SD= 8.3322	t= -12.829 p= .000*
Education	M= 9.6845 SD= 4.5296	M= 15.6060 SD= 2.5993	t= -29.360 p= .000*
Sex (% Females)	69%	58%	X^2 = 18.451 p= .000*
APOEε4 Status	Absent= 82.62% Present= 17.38%	Absent= 71.80% Present= 28.20%	X^2 = 21.692 p= .000*
GDS Total	M= 6.222 SD= 6.324	M= 4.357 SD= 6.572	F= 24.979 p= .000*
GDS Dysphoria	M=1.986 SD= 2.540	M= 1.169 SD= 2.639	F= 29.651 p= .000*
GDS Meaningless	M= .765 SD= 1.422	M= .583 SD= 1.472	F= 3.636 p= .058
GDS Apathy	M= 1.367 SD= 1.702	M= 1.206 SD= 1.776	F= 2.171 p= .141
GDS Cognitive Impairment	M= 2.104 SD= 1.829	M= 1.399 SD= 1.903	F= 42.386 p= .000*

* $p<0.05$.

Table 2 presents the level of each biomarker for each group. NHWs have significantly higher levels of $A\beta_{40}$ than MAs whereas MAs have significantly higher levels of total Tau, and $A\beta_{42}$/ $A\beta_{40}$ ratio. For the total sample GDS total score was significantly related to $A\beta_{42}$ (r= .065, p= .009) and Tau (r= .083, p= .001). There was no relationship between $A\beta_{40}$ (r= .039, p= .119), NfL (r= .032, p= .194) and the $A\beta_{42}$/ $A\beta_{40}$ ratio (r= .001, p= .987) and GDS total score. For the MA sample, there were small but significant correlations between GDS total score and $A\beta_{40}$ (r= .100, p= .011), $A\beta_{42}$ (r= .110, p= .005) and NfL (r= .125, p= .002) but not with Tau (r= .070, p= .077) or $A\beta_{42}$/ $A\beta_{40}$ ratio (r= -.023, p= .555). For the NHW sample none of the correlations between GDS total score and the biomarkers reached significance ($A\beta_{40}$ (r= .072, p= .067), $A\beta_{42}$ (r= -.007, p= .862), tau (r= .036, p= .362), NfL (r= .010, p= .805), ($A\beta_{42}$/ $A\beta_{40}$ ratio (r= -.069, p= .079).

Table 2. Level of Biomarkers by Ethnicity

Biomarkers	Mexican Americans N= 645	Non-Hispanic Whites N= 644	
$A\beta_{40}$	M= 236.39 SD= 64.112	M= 265.00 SD= 64.279	F= 11.762 P= .001*
$A\beta_{42}$	M= 11.779 SD= 3.377	M=12.190 SD= 3.129	F= .396 P= .529
Total Tau	M= 2.551 SD= .912	M= 2.329 SD= .934	F= 9.808 P= .002*
NFL	M= 19.894 SD= 10.978	M= 16.453 SD= 11.458	F= .169 P= .681
$A\beta_{42}$/ $A\beta_{40}$	M= .0514 SD= .0153	M= .0473 SD= .0133	F= 15.780 P= .000*

*$p \leq .05$

Regression models were constructed to assess the ability of the biomarkers to predict GDS scores. Age, sex, education and APOEε4 status were included as predictor variables. APOEε4 status was included as a predictor, as it is the single strongest genetic risk for Alzheimer's. For the entire sample, only NfL (t= 2.248, p= .025) was a significant predictor of GDS total score and also significantly predicted scores on the subscale of

Dysphoria (t= 2.087, p= .037). None of the other biomarkers had a significant relationship to GDS total or any of the subscales. When regression models were constructed for the two ethnic groups separately, it was found for MAs that NfL levels predicted GDS total score (t= 2.368, p= .018) along with the Dysphoria subscale (t= 2.555, p= .011). Linear regression analyses for the NHW group found $A\beta_{40}$ significantly predicted GDS total score (t= 2.114, p= .035) and the Dysphoria subscale score (t= 2.023, p= .044). For both groups there was no relationship between GDS total score and any of the other subscales and $A\beta_{42}$, total Tau or $A\beta_{42}/ A\beta_{40}$ ratio.

To assess the impact of level of depressive symptoms on the relationship to the plasma biomarkers, participants were divided into depressed and non-depressed based on the clinical cut off for depression of 10 on the GDS 30 total score. When the sample is considered as a whole (Table 3), 1076 participants endorsed fewer than 10 GDS items and were classified as non-depressed and 213 participants endorsed 10 or more items and were classified as depressed. The difference between depressed and non-depressed in the level of each biomarker was evaluated using ANOVA. The depressed group had significantly higher levels of $A\beta_{40,}$ $A\beta_{42}$ and NfL than those classified as non-depressed. The two groups did not differ on total Tau or $A\beta_{42}/ A\beta_{40}$ ratio.

Table 3. Biomarkers Comparing Non-Depressed with Depressed

Biomarkers	Non-Depressed N= 1076	Depressed N= 213	
$A\beta_{40}$	M= 249.205 SD= 65.573	M= 257.714 SD= 66.318	F= 9.310 P= .002*
$A\beta_{42}$	M= 11.920 SD=3.199	M= 12.337 SD= 3.548	F= 4.528 P= .024*
Total Tau	M= 2.415 SD= .899	M= 2.564 SD= 1.059	F= 1.097 P= .295
NFL	M= 17.943 SD= 10.995	M= 19.275 SD= 12.961	F= 7.072 P= .008*
$A\beta_{42}/ A\beta_{40}$	M= .0494 SD= .0149	M= .0490 SD= .0119	F= 1.262 P= .261

* $p<0.05$

Table 4 shows the comparison of the non-depressed to depressed by ethnic group. A significantly higher percentage of MAs scored in the depressed range (χ^2 =13.413, p= .000). For MAs, those endorsing 10 or more symptoms of depression had significantly higher levels of $A\beta_{40,}$ $A\beta_{42}$ and NfL than the non-depressed group with no difference found for total Tau. The NHW depressed group did not differ from the non-depressed group on any of the biomarkers. ANOVAs co-varying age, education sex and APOEε4 status comparing biomarkers levels for the two depressed groups showed that the depressed NHWs had a significantly higher level of $A\beta_{40}$,(F= 24.370, p= .000) than the depressed MAs. The depressed MAs had significantly higher levels of total Tau (F= 14.844, p= .016) than the NHWs who scored in the depressed range. There were no significant differences between depressed MAs and depressed NHWs on the level of $A\beta_{42}$ (F= 1.043, p= .698), NfL(F= .151, p= .698) or $A\beta_{42}/ A\beta_{40}$ ratio (F= 10.551, p= .109).

DISCUSSION

The current findings strongly support the importance of evaluating the effect of ethnicity when assessing the relationship of AD biomarkers to depression. There was no overlap in the biomarkers significantly related to depression for NHWs and MAs. The relationship of depressive symptoms to the AD biomarkers was distinct for the two groups. Although NfL was a significant predictor of depressive symptoms for the overall cohort, this relationship held only for the MA sample. For MAs NfL, a biomarker of global deterioration was related to overall GDS scores and scores on the Dysphoria scale, which consists of items directly related to sad or depressed mood. For NHWs, total GDS and Dysphoria scores were related to $A\beta_{40}$, a marker of amyloid burden. Apathy which was found to be related to Aβ pathology in the early stage of Alzheimer's in a Swedish study[35] was not be related either marker of amyloid in our cohort.

Table 4. Biomarkers Comparing Non-Depressed with Depressed by Ethnicity

Mexican American	Non-Depressed N= 514	Depressed N= 131	
$A\beta_{40}$	M= 233.697 SD= 64.083	M= 246.969 SD= 64.112	F= 4.896 P= .027*
$A\beta_{42}$	M= 11.597 SD= 4.625	M= 12.493 SD= 5.225	F= 7.592 P= .006*
Total Tau	M= 2.516 SD= 1.215	M= 2.688 SD= 1.542	F= 2.100 P= .148
NFL	M= 15.985 SD= 15.515	M= 18.276 SD= 18.491	F= 2.267 P= .039*
$A\beta_{42}$/ $A\beta_{40}$	M= .0513 SD= .0161	M= .0515 SD= .0119	F= .003 P= .955
Non-Hispanic Whites	Non-Depressed N= 562	Depressed N= 82	
$A\beta_{40}$	M= 263.570 SD= 63.701	M= 274.878 SD= 67.692	F= 3.384 P= .066
$A\beta_{42}$	M= 12.205 SD= 3.105	M= 12.088 SD= 3.305	F= .006 P= .936
Tau	M= 2.324 SD= .928	M= 2.365 SD= .934	F= .003 P= .953
NFL	M= 19.750 SD= 10.729	M= 20.872 SD= 12.572	F= 2.432 P= .120
$A\beta_{42}$/ $A\beta_{40}$	M= .0476 SD= .0136	M= .0449 SD= .0107	F= 2.730 P= .099

* $p<0.05$

When the level of depression as measured by the number of GDS items endorsed is analyzed for the total sample, those defined as depressed had higher levels of $A\beta_{40}$, $A\beta_{42}$ and NfL. Previously it has been shown higher amyloid beta[36]and NfL[37]are related to late life depression, however these studies did not consider the possible impact of ethnicity on this relationship. In the current study, ethnicity was a significant factor as the depressed MA group had higher levels each of these AD biomarkers than non-depressed MAs. For the NHW sample, there were no significant differences between depressed and non-depressed in biomarker levels for any of the biomarkers. This suggests that the relationship of depression to the AD biomarkers under study may be more of a factor for MAs with higher levels of depression. Identifying this subgroup, who maybe at higher risk for cognitive decline, early by assessing depression symptoms and biomarker profile could lead to a precision medicine approach to treating and preventing cognitive loss.

Consistent with what we have previously shown,[36,37] the presence APOEε4 is significantly higher in NHWs than MAs. Although the presence of APOEε4 has been linked to poorer performance in multiple cognitive domains in NHWs and poorer memory in MAs [38], and is a major risk for the development of dementia, there is evidence that APOEε4 positivity does not confer increased risk for depression[39]. Our results are consistent with the lack of a relationship between depressive symptoms and APOEε4 status and this held for both NHWs and MAs.

Chan et al.[40] in a longitudinal study of depression and CSF biomarkers ($A\beta_{42}$, t-tau & p-tau) of AD found that higher levels of depression and lower levels of AD biomarkers were related to progression to MCI. In our cross sectional study, individuals with a higher level of depression had higher levels of the blood-based biomarkers but this relationship held only for MAs. Longitudinal research with this population would clarify whether higher level of depression along with higher blood based biomarkers is a better predictor of cognitive decline for MAs than depression or the biomarkers alone.

Prior work has linked tau accumulation as measured by tau PET with major depression using the GDS to assess symptom severity.[41]Depression has been associated with tau but not amyloid in a study of PET imaging and depression.[42] In the current research in those with unimpaired cognition, plasma Tau was not related to level of depressive symptoms as measured by the GDS for either MAs or NHWs. We are currently collecting PET tau data on our cohort that will allow us to determine the role of tau in depression and the impact of ethnicity on that relationship. Other blood-based biomarkers of

tau such as ptau181 also need to be investigated to clarify the tau-depression association.

The current research is one of the few to study the AD biomarker- depression relationship in MAs in comparison to NHWs. Although the sample size was robust and community based, there are a number of limitations that effect the generalizability of the findings. Our sample consisted of only MA and NHW and comparisons with other racial and ethnic groups could not be done. To allow for further comparisons our group is currently engaged in a community based longitudinal study of the three most populace ethnic/racial groups in America with samples of 1000 Mexican Americans, 1000 African Americans and 1000 Non-Hispanic Whites. The current study utilized cross-sectional data and the nature of changes over time and the impact of the biomarker - depression relationship on the progression of cognitive decline could not be assessed. The ongoing longitudinal research will allow us to clarify the effect of these variables on the biomarker-depression relationship. The study utilized a single measure of depressive symptoms rather than clinically determined diagnosis of depression. We utilized clinical rather than biomarker based criteria for diagnostic assignment that may have had an impact on the validity of our diagnoses. The problem of diagnostic validity will be resolved in the ongoing study that includes amyloid imaging for diagnosis. Even with these limitations, the current research strongly supports the need to consider ethnic differences when evaluating the relationship of AD biomarkers to depression.

Conclusions: Depression is both a risk for and early symptom of Alzheimer's. The current research examined the relationship of plasma biomarkers of Alzheimer's and depressive symptoms and found that both ethnicity and level of depression affected the biomarker profile. The use of plasma biomarkers that have been related to depression and cognitive disorders to identify those at risk for cognitive decline will need to take ethnicity into account to increase accuracy.

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STATEMENT OF ETHICS

This project was conducted under University of North Texas Health Science Center IRB approved protocols and is in accordance with Code of Ethics of the World Medical Association Declaration of Helsinki.

CONFLICTS OF INTEREST

SEO has multiple patents on precision medicine for neurodegenerative diseases. None of the other authors report conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the creation and writing of this manuscript, agree with the findings and have given consent to include their names on this manuscript. JRH was involved in designing the project, writing and revising the manuscript, MP reviewed and made substantial edits to the manuscript, LAJ was involved in reviewing and editing the manuscript, SEO was involved designing the project and writing the manuscript.

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