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Sex Differences in Plasma Biomarkers of Alzheimer's Disease in a Diverse Community Cohort: A HABS-HD Study

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Abstract

Background: There has been increased research investigating the utility of plasma biomarkers of Alzheimer's disease as diagnostic markers, predictors of risk and progression. Although there is extensive evidence pointing to sex differences in epidemiology, vulnerability, pathology and progression of AD there is a dearth of research on the impact of sex differences on Alzheimer's related plasma biomarkers. There exists limited research on the impact of ethnicity on these biomarkers. Current research investigated sex differences in plasma biomarkers of amyloid ($A\beta_{40}$, $A\beta_{42}$), tau (total tau) and neurodegeneration (Neurofilament Light Chain (NFL)) in older Mexican Americans and non-Hispanic Whites.

Method: Sample included 292 male and 561 female Mexican Americans and 354 male and 430 female non-Hispanic Whites from Health and Aging Brain Study-Health Disparities (HABS-HD) study. Plasma samples were assayed using Simoa technology. Sex and ethnic differences for the biomarkers were assessed using ANOVAs co-varying for age.

Results and Discussion: Significant main effects were found for $A\beta_{40}$ and tau for sex and ethnicity. Males had higher $A\beta_{40}$ than females while females had higher tau. Non-Hispanic Whites had higher $A\beta_{40}$ than Mexican Americans and lower total tau. Mexican American females had higher tau and lower NFL than Mexican American males. Non-Hispanic White females had higher tau than non-Hispanic White males who had higher $A\beta_{40}$. Non-Hispanic White males had higher $A\beta_{40}$ than Mexican American males who had higher tau and $A\beta_{42}/A\beta_{40}$ ratio. Non-Hispanic White females had higher $A\beta_{40}$ than Mexican American females while Mexican American females had higher tau and $A\beta_{42}/A\beta_{40}$ ratio.

Conclusion: Findings reveal sex differences, ethnic differences, sex differences within ethnic groups and ethnic differences within the same sex in concentrations of plasma biomarkers. The use of AD plasma biomarkers as screening tools, diagnostic markers and trial endpoints need to consider sex and ethnic differences.

Keywords: Sex differences; Plasma biomarkers; Alzheimer's disease; Ethnicity

Introduction

The AT(N) framework provides a biologically based approach to understand the nature of Alzheimer's and its diagnosis and progression [1]. Initially the AT(N) framework emphasized imaging and Cerebrospinal Fluid (CSF) biomarkers as reflecting the nature of the pathological processes underlying Alzheimer's Disease (AD). Subsequently there has been an increased interest in blood-based biomarkers of these processes due to the cost-effective, minimally invasive and highly scalable nature of these biofluids [2]. The advent of new assay technology has made the reliable assessment of plasma biomarkers of amyloid, tau and neurodegeneration possible. These plasma markers of have been investigated as diagnostic markers, predictors of risk and disease progression [3-13]. Although there has been a significant increase in research investigating the utility of plasma biomarkers there are a number of gaps in our understanding of the factors influencing the level of these biomarkers.

There is strong evidence supporting the presence of sex differences in the epidemiology, vulnerability, pathology and progression of Alzheimer's disease, however there is limited research on the impact of sex differences on Alzheimer's related plasma biomarkers such as $A\beta_{40}$, $A\beta_{42}$, total tau (t-tau) and Neurofilament Light (NFL) [14-19]. Sex differences have been found to effect the trajectory over time of plasma NFL and t-tau in individuals with subjective memory complaints [20]. Sex differences in plasma tau concentration with males having higher levels have been found [21]. Although few studies have assessed sex differences in plasma $A\beta_{40}$ and $A\beta_{42}$, a study on $A\beta_{42}$ plasma levels in healthy adults found no sex differences [22]. Significant sex differences were found for Simoa plasma $A\beta_{40}$ in a British cohort [23]. The assessment and reporting of the presence or absence of sex differences in plasma biomarkers remains a priority to determine the utility of these blood-based biomarkers in the detection and treatment of AD [24].

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Another gap in our understanding of factors effecting the level of plasma biomarkers is the impact of ethnicity [25]. The majority of research on plasma biomarkers has been conducted on non-Hispanic Whites in clinical settings. In one of the few studies looking at differences in plasma NFL concentrations in a biracial community sample, higher levels were found among whites compared to African Americans [26]. A study of plasma biomarkers in African Americans including tau and $A\beta_{42}$ comparing cognitively unimpaired individuals with Alzheimer's patients found that tau was significantly higher in the AD group and $A\beta_{42}$ level was not associated with Alzheimer's [27]. Our previous research of a community-based, ethnically diverse cohort has shown that the level of NFL and factors that effect plasma biomarkers such as medical comorbities are influenced by ethnicity/race [28,29]. A recent study found that the levels of $A\beta_{40}$, $A\beta_{42}$, total tau and neurofilament light (NFL) for African Americans were significantly lower than for Non-Hispanic Whites (NHW) and Mexican Americans (MA) had higher levels of total tau than Non-Hispanic Whites [30]. These findings support the importance of ethnicity/race in any study utilizing blood bio-fluid biomarkers. In these studies of the impact of ethnicity, sex was treated as a co-variant and sex differences in biomarkers were not reported. To help clarify the nature of sex differences in diverse populations, the current study investigated the presence of sex differences in plasma biomarkers of amyloid ($A\beta_{40}$, $A\beta_{42}$), tau (total tau) and neurodegeneration NFL in a community based sample of older Mexican Americans and Non-Hispanic Whites.

Materials and Methods

Participants and assessment

The sample consisted of 1637 participants from the Health and Aging Brain Study-Health Disparities study (HABS-HD; formally the Health and Aging Brain study among Latino Elders, HABLE study). The HABS-HD study is an ongoing, longitudinal, community-based project examining health disparities in aging and cognitive decline among Mexican Americans as compared to non-Hispanic whites with recent expansion to enroll African Americans. The current sample included 292 males and 561 females self-identified as Mexican Americans and 354 males and 430 females self-identified as non-Hispanic Whites.

The HABS-HD methods have been published elsewhere and are briefly outlined below. Participant recruitment utilizes a Community-Based Participatory Research (CBPR) approach [31,32]. The HABS-HD protocol includes an interview, functional exam, blood draw for clinical labs and biobanking, neuropsychological testing and 3T MRI of the brain. Amyloid and tau Positron Emission Tomography (PET) scans are currently underway in the cohort. All aspects of the study protocol can be conducted in Spanish or English. This study protocol was reviewed and approved by the University of North Texas Health Science Center Institutional Review Board (UNTHSC IRB) protocols UNTHSC 2016-128 and 2020-125. Each participant (or his/her legal representative) signed written informed consent to participate in the study. All HABS-HD data is available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website [33].

Blood collection and processing procedures

Collection and processing of blood samples were completed based on the international guidelines for AD biomarker studies and processed within 2 hours (stick-to-freezer) [34]. Samples were assayed in the university of north texas health science center Institute for Translational Research (ITR) laboratory by the ITR biomarker core. hamilton robotics easyblood was utilized for blood processing, aliquoting and re-aliquoting. All plates were prepared using a custom hamilton robotics starplus system. assays were run on a multi-plex biomarker platform using Electrochemiluminescence (ECL).

Samples

500 µL of plasma were used to measure biomarker levels using the Single Molecule Array (SIMOA) technology (Simoa; Quanterix, Lexington, MA, USA). Optimized dilution factors and centrifugation were determined and the suggested dilution factor of 4x was used. After thawing, the samples were vortexed and spun at 10,000 g 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 0.038 pg/mL.

Multiplexed detection of $A\beta_{42}$, $A\beta_{40}$ and Total tau also utilized SIMOA technology. LLODs for $A\beta_{42}$, $A\beta_{40}$ and Total tau were reported at 0.045 pg/mL, 0.196 pg/mL, 0.019 pg/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=0.0-); Total tau (High control CV=0.040, Low control CV= 0.047; NFL (high control CV= 0.035, Low control CV= 0.092).

Statistical analysis

Statistical analysis were conducted in SPSS 25 International Business Machines (IBM). Demographic variables were analyzed using T tests for independent samples. Sex differences for the biomarkers were assessed using ANOVA co-varying age.

Results and Discussion

Table 1 presents the characteristics of the sample by sex and ethnicity. For the total sample 39.5% were males who were significantly older and had significantly more years of education than the female participants had both the NHW males and females were significantly older than their MA counterparts (males t=7.753, p=0.000, df=644; females t=10.249, p=0.000, df=998) and had significantly more years of education (males t= 20.455, p=0.000; df=644; females t=24.699, p=0.000, df=989). Within the groups, there was no difference in age between NHW males compared to the NHW females, although males had significantly more years of education. For MA, there was no difference in education but males were significantly older.

Characteristics	Male	Female	p-value
Total Sample	N=646	N=991	-
Age	M=67.506	M=65.799	t=3.838
	SD=8.743	SD=8.868	p=0.000*
Education	M=13.043	M=11.891	t=4.585
	SD=5.447	SD=4.608	p=0.000*
Mexican American	N=292	N=561	-
Age	M=64.650	M=63.491	t=2.017
	SD=7.874	SD=7.999	P=.044*
Education	M=9.485	M=9.419	t=0.199
	SD=5.054	SD=4.337	p=.843
Non-Hispanic White	N=354	N=430	-

Age	M=69.757	M=68.896	t=1.382
	SD=8.758	SD=8.616	p=.167
Education	M=15.865	M=15.163	t=3.838
	SD=2.710	SD=2.408	p=0.000*
Note: *: ≤0.050.			

Table 1: Characteristics of the sample.

Table 2 presents the comparison of males and females on the level of each of the biomarkers for the total sample. Males had significantly higher levels of $A\beta_{40}$ than females while females had significantly higher levels of total tau. There was no difference between the sexes on the level of $A\beta_{42}$ or NFL. Males and females did not differ on $A\beta_{42}/A\beta_{40}$ ratio.

Characteristics	Male	Female	p-value
	N=646	N=991	
$A\beta_{40}$	M=258.295	M=249.054	F=7.833
	SD=65.117	SD=65.227	p=0.005*
	95% CI=253.269,263.321	95% CI=244.989,253.119	-
$A\beta_{42}$	M=12.184	M=11.991	F=1.365
	SD=3.253	SD=3.274	p=0.243
	95% CI=11.933,12.436	95% CI=11.788,12.195	-
Total tau	M=2.260	M=2.628	F=47.729
	SD=0.951	SD=1.153	p=0.000*
	95% CI=2.170, 2.337	95% CI=2.564,2.699	
NFL	M=20.562	M=18.553	F=2.907
	SD=16.690	SD=13.847	p=0.088
	95% CI=19.023,21.035	95% CI=18.089, 19.716	-
$A\beta_{42}/A\beta_{40}$ ratio	M=0.0485	M=.0497	F=2.687
	SD=0.0121	SD=0.0153	p=0.101
	95% CI=0.047,0.050	95% CI=0.049,0.051	-
Note: *: ≤ 1.050.			

Table 2: Biomarkers by sex for the total sample.

The level of the biomarkers by ethnicity for the total sample are shown in Table 3. The NHW group had significantly higher levels of $A\beta_{40}$ than MA and significantly lower levels of total tau. There was no difference between the two groups on the level of $A\beta_{42}$ or NFL. MA had a significantly higher $A\beta_{42}/A\beta_{40}$ ratio than NHW. Analysis of each of the biomarkers assessing ethnicity and sex revealed significant main effects for $A\beta_{40}$ (Ethnicity F(1,1625)=21.037; p=0.000; Sex F(1,1625)= 6.022, p=0.014) and t-tau (Ethnicity F(1,1625)=20.890; p=0.000;Sex F(1,1625)=42.036, p=0.000) only.

Characteristics	Mexican Americans	Non-Hispanic Whites	p-value
	N=853	N=784	
$A\beta_{40}$	M=245.015	M=261.822	F=21.037
	SD=68.487	SD=66.704	p=0.000*
	95% CI=240.563, 249.467	95% CI=256.627,265.979	
$A\beta_{42}$	M=11.878	M=12.296	F=1.242
	SD=3.497	SD=3.339	p=0.265
	95% CI=11.749, 12.219	95% CI=11.915, 12.362	
Total tau	M=2.575	M=2.313	F=20.880
	SD=1.136	SD=1.087	p=0.000*
	95% CI=2.541,2.691	95% CI=2.258,2.415	
NFL	M=19.352	M=19.649	F=0.184
	SD=13.986	SD=13.410	p=0.668
	95% CI=18.659,20.542	95% CI=18.236,20.029	
$A\beta_{42}/A\beta_{40}$ ratio	M=0.0512	M=.0471	F=33.195
	SD=0.0148	SD=.0129	p=0.000*
	95% CI=0.050,0.052	95% CI=0.046,0.048	
Note: *: ≤ 0.05.			

Table 3: Biomarkers by ethnicity for the total sample.

Table 4 presents the biomarkers by sex for the two ethnic groups. A comparison of the sexes within each ethnic group revealed that MA females had significantly higher total tau and significantly lower NFL than MA males with no difference between the sexes on the level of either of the amyloid markers. Male and female MA did not differ on $A\beta_{42}/A\beta_{40}$ ratio. As was the case with MA females, NHW females had significantly higher total tau than the NHW males whereas NHW males had significantly higher $A\beta_{40}$ than NHW females. The difference in the $A\beta_{42}/A\beta_{40}$ ratio approached significance with females having a higher ratio.

Non-Hispanic Whites	Male	Female	p-value
	N=354	N=430	
$A\beta_{40}$	M=273.537	M=262.248	F=4.448
	SD=69.409	SD=61.333	p=0.035*
$A\beta_{42}$	95% CI=269.019,279.123	95% CI=257.086,269.010	-
	M=12.372	M=12.185	F=0.271
	SD=3.402	SD=3.034	p=0.603
	95% CI=12.006,12.661	95% CI=11.918,12.514	-
Total tau	M=2.136	M=2.557	F=30.419
	SD=0.839	SD=1.213	p=0.000*
	95% CI=2.024,2.246	95% CI=2.256,2.658	-
NFL	M=21.891	M=20.558	F=0.765
	SD=16.845	SD=10.392	p=0.382
	95% CI=20.263,22.950	95% CI=19.568,22.022	
$A\beta_{42}/A\beta_{40}$ ratio	M=0.0461	M=0.0479	F=3.673
	SD=0.0104	SD=0.0147	p=0.056
	95% CI=0.045,0.047	95% CI=0.047,0.049	-
Mexican Americans	Male	Female	-
	N=292	N=561	

$A\beta_{40}$	M=245.261	M=236.494	F=1.928
	SD=108.329	SD=90.120	p=0.165
	95% CI=236.245, 251.509	95% CI=231.712, 242.718	-
$A\beta_{42}$	M=12.143	M=11.740	F=1.394
	SD=5.220	SD=4.757	p=0.238
	95% CI=11.681,12.452	95% CI=11.502,12.058	-
Total tau	M=2.413	M=2.681	F=13.841
	SD=1.492	SD=1.563	p=0.000*
	95% CI=2.276,2.523	95% CI=2.599,2.778	-
NFL	M=18.995	M=17.002	F=3.941
	SD=13.824	SD=13.761	p=0.049*
	95% CI=17.144,20.177	95% CI=16.126,17.034	-
$A\beta_{42}/A\beta_{40}$ ratio	M=0.0512	M=0.0512	F=0.000
	SD=0.0187	SD=0.0211	p=0.990
	95% CI=0.049,0.053	95% CI=0.050,0.052	-
Note: *: ≤ 0.05.			

Table 4: Biomarkers by sex by ethnicity.

A comparison of the same sex across ethnicity showed a significant difference for $A\beta_{40}$ with NHW males having a significantly higher concentration (F(1,641)=7.456, p=0.006) than MA males. MA males had a significantly higher level of total tau than NHW males (F(1,641)=17.719, p=0.000). A significant difference in the $A\beta_{42}/A\beta_{40}$ ratio was found with MA males having a higher ratio (F(1,641)=27.839, p=0.000). There was no difference between the male ethnic groups for $A\beta_{42}$ (F(1,641) = 1.360, p =0.244) or NFL (F(1,641)=0.056, p =0.813).

NHW females had significantly higher $A\beta_{40}$ than MA females (F(1,983) = 13.966, p=0.000). MA females had significantly higher total tau than NHW females (F(1,983)=6.119, p=0.014). A significant difference in the $A\beta_{42}/ A\beta_{40}$ ratio was found with MA females having a higher ratio (F(1,983)=11.115, p=0.001). There was no difference between the female ethnic groups for $A\beta_{42}$ (F(1,983)=0.102, p=0.750) or NFL (F(1, 983)=0.296, p=0.586).

In the current research, sex differences in concentrations of plasma biomarkers were found for the total sample with males having a significantly higher level of $A\beta_{40}$ and females having a higher level of t-tau. There is limited research reporting sex differences for either plasma $A\beta_{40}$ or $A\beta_{42}$. The finding of sex differences in plasma total tau is consistent with Pase and Baldacci [6,20] although others have not found a difference [35,36]. Sample differences may account for this discrepancy. The lack of sex differences in plasma NFL in the overall sample is consistent with previous research [20,37]. There is no available research on sex differences in the plasma $A\beta_{42}/A\beta_{40}$ ratio, although research on CSF has shown no difference between the sexes [38].

In addition to sex differences there were significant ethnic differences. In the comparison of the level of the plasma biomarkers between the two ethnic groups, NHW had significantly higher $A\beta_{40}$ than MA and the level of total tau for MA was significantly higher than NHW. The MA sample had a significantly higher $A\beta_{42}/A\beta_{40}$ ratio. As was found with sex there were no ethnic differences in the concentrations of $A\beta_{42}$ or NFL for the total sample.

Sex differences within each ethnic group were found with females for both groups having significantly higher levels of total tau than males. Although NHW males had significantly higher plasma $A\beta_{40}$ than NHW females, this sex difference was not found in the MA sample. MA females had a higher level of NFL than male MA. When comparing the concentration of the biomarkers within the same sex across ethnic groups a number of differences were found. Both NHW males and females had significantly higher $A\beta_{40}$ than there MA counterparts. The level of t-tau was significantly higher for both MA males and females compared to NHW males and females, as was the $A\beta_{42}/A\beta_{40}$ ratio [39].

Conclusion

The findings of the current study of concentrations of plasma biomarkers of AD reveal sex differences, ethnic differences, sex differences within ethnic groups and even ethnic differences within the same sex. This research is descriptive and does not posit any biological or socio-cultural reasons for our findings but points to the complexity of the factors that may influence concentrations of plasma biomarkers and their use. The current findings underscore the difficulty of developing standard cut points for these biomarkers given sex and ethnic differences. The development of useful normative values for the biomarkers specific to each sex would also need to consider ethnic differences.

The sample of two of the largest ethno-racial groups in the US studied in this research was relatively large and community based. However, given the presence of ethnic group differences the addition of representation from other groups including African Americans would be important. The goal of the HABS-HD study is to recruit 1000 older African Americans along with 1000 MA and 1000 NHW, to allow additional comparisons. The current study relied on self-report of sex and treated sex as a binary variable. It has been argued that doing so may under represent sex minority populations with possible biological differences. Even with these limitations, given the efforts to utilize blood-based AD biomarkers as screening tools, diagnostic markers and trial endpoints, the current findings on sex and ethnic differences have direct applicability to these efforts.

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