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The impact of comorbid depression – diabetes on proteomic outcomes among community-dwelling Mexican Americans with Mild Cognitive Impairment

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Abstract

Background: Mexican Americans suffer from a disproportionate burden of modifiable risk factors, which may contribute to the health disparities in MCI and AD.

Objective: The purpose of this study was to elucidate the impact of comorbid depression and diabetes on proteomic outcomes among community-dwelling Mexican American adults and elders.

Methods: Data from participants enrolled in the Health and Aging Brain among Latino Elders (HABLE) study was utilized. Participants were 50 or older and identified as Mexican American (N= 514). Cognition was assessed via neuropsychological test battery and diagnoses of MCI and AD adjudicated by consensus review. The sample was stratified into four groups: Depression only, Neither depression nor diabetes, Diabetes only, and Comorbid depression and diabetes. Proteomic profiles were created via Support Vector Machine (SVM) analyses.

Results: In Mexican Americans, the proteomic profile of MCI may change based upon the presence of diabetes. The profile has a strong inflammatory component and diabetes increases metabolic markers in the profile.

Conclusion: Medical comorbidities may impact the proteomics of MCI and AD, which lend support for a precision medicine approach to treating this disease.

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Author contributions

Conceived and designed the experiments: LAJ, FZ, SEL, JRH & SO. Performed the experiments: LAJ, FZ, SEL, JRH & SO. Analyzed the data: LAJ, SEL, FZ. Contributed reagents/materials/analysis tools: LAJ, SEL, FZ, JRH & SO. Wrote the manuscript: LAJ, SEL, FZ, JRH & SO. Other: ICMJE criteria for authorship read and met: LAJ, SEL, FZ, JRH & SO. Agree with manuscript results and conclusions: LAJ, SEL, FZ, JRH & SO.

Conflict of Interest/Disclosure Statement

Dr. Sid O'Bryant has pending patents related to his Alzheimer's disease blood test. UNTHSC has licensed these patents to CX Precision Medicine, Inc. Dr. O'Bryant has a financial interest in this company and is the Chief Scientific Advisor. CX Precision Medicine had no role in the design or results of this study.

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Keywords

Mexican Americans; Diabetes Mellitus; Depression; Proteomics

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative dementia, and over 5.7 million Americans are living with a diagnosis of AD (Alzheimer's Association, 2017). AD is the 6th leading cause of death in the US, and the costs associated with care for the disease are estimated to be $277 billion (Alzheimer's Association, 2017). As the population ages, the prevalence of AD is expected to grow dramatically, with estimates reaching up to 14 million by 2050 (Alzheimer's Association, 2017). Mexican Americans are one of the fastest aging populations in the US, and are at increased risk of developing AD or mild cognitive impairment (MCI) (Alzheimer's Association, 2017; Jacobsen *et al.,*2011; Novak and Riggs, 2004). Mexican Americans develop MCI and AD at younger ages and when they are diagnosed with cognitive impairment, they are diagnosed at more advanced stages. (O'bryant *et al.,*2013a; O'bryant *et al.,*2007; O'Bryant *et al.,*2013b). Mexican Americans have higher rates of modifiable risk factors such as diabetes and depression have a lower frequency of the ApoEε4 allele as well as demonstrating an AD proteomic profile that is metabolic in nature (O'bryant *et al.,*2013a; O'Bryant *et al.,*2013b; Sundquist and Winkleby, 1999; Haan *et al.,*2003; O'Bryant *et al.,*2013c). Despite the demonstrated medical, genetic and proteomic differences among Mexican Americans diagnosed with MCI and AD as compared to non-Hispanic whites, there is a dearth of literature investigating biological mechanisms and pathways for AD among this group (O'Bryant *et al.,*2013c; O'Bryant *et al.,* 2010; O'Bryant *et al.,*2013d). Therefore, the goal of this study was to elucidate the impact of comorbid depression and diabetes on proteomic outcomes among community-dwelling Mexican American adults and elders.

Depression and diabetes mellitus (DM) are two AD risk factors which are more prevalent among Mexicans Americans. Individually both depression and diabetes have been linked to cognitive decline. Multiple epidemiological studies such as the Rotterdam Study, the Framingham Heart Study, the Honolulu-Asia Aging Study, and the Religious Orders Study have found DM increased the risk for AD, MCI, and cognitive dysfunction (Ott *et al.,*1996; Ott *et al.,*1999; Elias *et al.,*2005; Pelia *et al.,*2002; Arvanitakis *et al.,*2004). Mexican Americans diagnosed with MCI and AD consistently have higher rates of type two diabetes mellitus (Gerst *et al.,*2010; Luchsinger *et al.,*2007; Palmer *et al.,*1996) and metabolic factors have been consistently strongly related to MCI among Mexican Americans (O'Bryant *et al.,* 2013a; Palmer *et al.,*1996). Research indicates type two diabetes mellitus impacts some of the basic pathological mechanisms of AD (de la Monte 2014; Kandimalla and Reddy, 2017). For example, insulin plays a role in the phosphorylation of tau and the formation of amyloid plaques, and insulin resistance has been hypothesized as a mechanism for cognitive decline (de la Monte, 2014; Kandimalla and Reddy, 2017). Both AD and type two diabetes mellitus are characterized by brain atrophy, reduced cerebral glucose metabolism, and insulin resistance (Verdile *et al.,*2015).

Depression, which is highly prevalent in Mexican Americans, is a modifiable risk factor for MCI and AD. Prior work has demonstrated that Mexican Americans suffer significantly higher rates of depression chronicity in the U.S. and significant gaps exist between depression diagnosis and treatment when compared to non-Hispanic whites (Gonzalez *et al.,* 2010; Hinton *et al.,*2012). Inflammation has been proposed as a biological pathway for the development of depression (Smith *et al.,*2018). In a population-based study in Rotterdam, higher IL6 (Interleukin 6) levels were strongly associated with depression among adults age 60. Of 1,686 participants age 70 and above from the Duke Established Population for Epidemiologic Studies of the Elderly (EPESE), serum IL6 was significantly associated with depression. In a recent meta-analysis, both IL-6 and CRP (C-reactive protein) were found to be associated with depression among older adults, and longitudinal data suggested that inflammation leads to depression rather than depression leading to inflammation (Smith *et al.,*2018; Tiemeier *et al.,*2013). A possible mechanism of action is that pro-inflammatory cytokines are able to cross the blood brain barrier and can affect structures such as the amygdala that regulate emotions (Smith *et al.,*2018). Depression increases risk for progression from MCI to AD, as well as risk for incident MCI over time (Modrego and Ferrandez, 2004; Barnes *et al.,*2006).

Both depression and diabetes are prevalent and often co-occurring conditions in the elderly, and researchers have found this co-morbidity significantly increased risk for MCI and AD across multiple cohorts (Downer, *et al.,*2016). However, the majority of this research has been conducted among non-Hispanic populations. The depression – diabetes comorbidity was associated with consistently increased risk for MCI and AD in Mexican Americans, but not non-Hispanic whites (Johnson *et al.,*2015). When examining proteomic profiles indicative of AD, our work has found that the proteomic profile of AD among Mexican Americans appears to be largely metabolic in nature as compared to a more inflammatory/vascular weighted AD profile found among non-Hispanic whites (O'Bryant, *et al.,*2013a; O'Bryant *et al.,*2013b). Again, when looking at proteomic markers, a combination of elevated depression and inflammation has been found to be associated with poorer memory performance among Mexican Americans. This work suggests that (1) depression and diabetes may be particularly important risk factors for MCI and AD among Mexican Americans, (2) there are proteomic differences in AD among Mexican Americans as compared to non-Hispanic whites, (3) Depression in combination with inflammation may further increase risk for cognitive loss and (4) inflammation may play a significant role in MCI among Mexican Americans, whereas a metabolic shift may occur in the transition to AD where the profile becomes more metabolic nature. In this study, we sought to examine the impact of depression and diabetes (alone and in combination) on the proteomic profile of MCI among Mexican Americans. An understanding of depression and diabetes can have significant implications as to which biological pathways are impacted by these conditions., These comorbid conditions may affect the interpretation of proteomic profiles associated with cognitive loss and MCI among Mexican Americans.

Materials and Methods

Participants

Data from 515 participants from the Health and Aging Brain among Latino Elders (HABLE) study were analyzed. The HABLE study is a community based, epidemiological study of cognitive aging among Mexican American adults and elders. Additional recruitment methods includes placing ads in local newspapers, distributing flyers and brochures through our community partners, snowball recruitment, and attendance at health fairs. Each participant underwent an interview (demographics, medical history, health behaviors), neuropsychological testing, fasting blood draw, and a medical examination. Additionally, all participants were required to name an informant that was willing and able to answer questions regarding their activities of daily living and cognition. Participants were interviewed in either English or Spanish, based on their preference. Cognitive diagnoses of MCI were assigned according to Mayo Clinic criteria, AD according to NINDS-ADRDA criteria, and normal controls were classified as participants who performed within normal limits on neuropsychological testing (Petersen and Negsh, 2008; McKhann *et al.,*2011). All diagnoses were determined through a consensus review panel. Diagnoses of depression and diabetes were also assigned by consensus review based on self-reported medical history (including medication status), fasting blood labs (glucose and HBa1c levels), and the 30-item Geriatric Depression Scale (GDS). This research was conducted under an Institutional Review Board approved protocol with each participant (and/or informants for cognitively impaired persons) providing written informed consent.

Blood Collection and Biomarker Analysis

Fasting blood samples were collected on all participants according to the recently published international guidelines (O'Bryant *et al.,*2015). The protocol for blood collection was: (1) fasting blood collected using 21g needle, (2) sample tubes collected in the following order – serum then plasma EDTA tube, (3a) serum tubes were allowed clot for 30 minutes at room temperature in a vertical position, (3b) plasma tubes were gently inverted 5–10 times, (4) centrifuged with horizontal rotor for 10 minutes at 2000 × g within one hour of collection, (5) 1.0 mL aliquots of serum was transferred into polypropylene (cryovial) tubes, (6) sample ID was affixed to each aliquot, and (7) samples were placed into −80° C freezer within 2 hours of collection. Electronic monitoring of each aliquot (i.e., location, number, sample use) was done via Freezerworks monitoring system. Temperature monitoring of all freezers was done via the Rees Scientific system (http://www.reesscientific.com/).

Proteomic analyses were conducted via electrochemiluminescence (ECL) using the MESO Scale Discovery Platform (MSD) based on our previously published protocol (O'Bryant *et al.,*2011). The MSD platform has been used extensively to assay biomarkers associated with a range of human diseases including AD. In our prior work, we conducted discovery and validation studies to identify and refine a putative AD blood profile (O'Bryant, et al.,2010; O'Bryant, et al.,2011; O'Bryant, et al.,2014; O'Bryant, et al.,2016). The AD algorithm consists of 21-proteins and has been validated across platforms, species and tissue type. Additionally, this 21-protein AD algorithm retains excellent diagnostic accuracy in detecting MCI and AD among Mexican Americans (Edwards *et al.,*2016). The proteins included in the

algorithm are as follows: fatty acid binding protein (FABP), beta 2 microglobulin, pancreatic polypeptide (PPY), macrophage inflammatory protein 1α (MIP1α), CRP, soluble vascular cell adhesion molecule-1 (sVCAM-1), thrombopoietin, α2 macroglobulin, eotaxin 3, tumor necrosis factor-alpha (TNF-α), tenascin C (TNC), interleukin-5 (IL-5), IL-6, IL-7, IL-10, IL-18, I309, Factor VII, thymus and activation-regulated chemokine (TARC), serum amyloid A (SAA), and soluble intercellular cell-adhesion molecule-1 (sICAM-1). All assays were conducted according to manufacture protocols; CVs nearly all assays were <10%. Average values and LLOD (lowest level of detection) for each marker from n=1,329 subjects have been published elsewhere (O'Bryant *et al.,*2016).

Statistical Analyses

The goal of the study was to examine the proteomic characteristics of Mexican Americans with comorbid depression and diabetes. Therefore, the cohort was divided into four groups: Neither (neither depression nor diabetes), Depression Only (depression in absence of diabetes), Diabetes Only (diabetes in absence of depression), and Comorbid (both depression and diabetes). Descriptive statistics can be found on Table 1. Our proteomic profile was created using Support Vector Machine (SVM) analyses with five-fold cross-validation with the models split by the four groups to determine the impact of depression and diabetes on the proteomic profiles as well as overall accuracy of the profile. SVM is a discriminative classifier that outputs an optimal hyperplane which categorizes new samples, given labeled training data. The advantage of five-fold cross-validation is that all the samples in the dataset are eventually used for both training and testing. The SVM model provides multiple performance measures: precision, accuracy, sensitivity, specificity, and AUC (area under the curve). The SVM model was performed using e1071 package in R (Version 3.3.3). The multiple performance measures are calculated as follows: precision = tp/(tp+fp); accuracy = (tp+tn)/(tp+tn+fp+fn); sensitivity = tp/(tp+fn); specificity = 1-fp/(fp+tn); tp is true positive, fp false positive, tn true negative, fn false negative. AUC is calculated using ROCR package in R.

Results

This study utilized data collected from 514 Mexican Americans in the Health and Aging Brain Study (normal control n=414, MCI n=100). The average age of participants was 60 years old. Participants were primarily tested in Spanish for 406 (78.8%) compared to English 109 (21.2%) participants. The sample consisted of 393 (76.3%) females and 122 (23.7) males. The marital status of the participants was 283 (55.0%) married, 104 (20.2%) divorced, 55 (10.7%) widowed, 47 (9.1%) separated, 23 (4.5%) never married and 3 (.6%) information not available. Descriptive statistics for the four groups (Neither, Depression only, Diabetes only, and Comorbid) can be found on Table 1.

SVM modeling was used to examine the impact of diabetes, depression, and comorbidity on our proteomic profile of MCI among Mexican Americans. Proteomic data were available from n= 414 cases (Diabetes only n=107; Depression only n=99; Comorbid n=69; Neither n=140) with consensus diagnoses of MCI (N=100) vs NC (N=414). Table 2 provides the accuracy statistics for all models. As can be seen, our proteomic profile achieves excellent

accuracy for all diagnostic groups/comorbidities for detecting MCI among Mexican Americans with all AUCs>=0.97. Even in the context of medical comorbidities, the accuracy was at 85% at the lowest with most models >=90%. Specificity was 0.99 – 1.0 for all models; however, sensitivity ranges from 0.42 – 0.85. As can be seen from Table 2, the optimal balance between SN and SP was found within the Depression Only group with SP = 0.99 and SN=0.85. With a 20% base rate of MCI among those age 65 and older (consistent with prior publications in community-based settings), this proteomic profile would yield a positive predictive value (PPV) of 0.96 and a negative predictive value (NPV) of 0.96. There are two primary results when examining the proteomic profile variable relative importance plots (Table 3). First, the proteomic profile of MCI among Mexican Americans appears to include a heavy inflammatory component, which is consistent with our recent work specifically examining a proteomic profile of amnestic MCI (Edwards *et al., (2016)*. Secondly, the presence of diabetes (with or without depression) introduces higher rankings of metabolic markers in the profile (e.g., pancreatic polypeptide, FABP). However, the Depression Only proteomic profile of MCI was largely inflammatory in nature, suggesting that medical comorbidities may not have tremendous impact on the overall accuracy of our proteomic profile, but the pathological mechanisms may vary and be additive in nature.

Discussion

Prior research has shown that both depression and diabetes impact cognitive function. The purpose of the current study was to investigate the impact of depression and diabetes on the proteomic profiles of individuals with Co-morbid Depression and diabetes, Depression only, Diabetes only, or Neither condition. This study found that Mexican Americans with MCI who had different comorbidities exhibited distinct biomarker profiles. The biomarker profile for MCI in the absence of depression or diabetes was predominately inflammatory; the biomarker profile for the presence of diabetes alone was primarily metabolic; the profile for depression alone was largely inflammatory, and the biomarker profile for the presence of both comorbidities included cardiovascular risk markers (ICAM, CRP).

Analysis of our previously established blood profile for detecting AD revealed that neither comorbidity had a substantial impact on the overall accuracy of the algorithm itself. That is, the presence of diabetes, depression or both only minimally impacted the overall accuracy of the algorithm. However, while specificity remained excellent across groups there was an impact on sensitivity. Additionally, the relative importance of the proteins within the algorithm changed by group (None, Depression only, Diabetes only, Comorbid). As has been noted in the literature, MCI is a heterogeneous categorization with multiple causes. Our results suggest that MCI due to metabolic dysfunction may be a novel subgroup biologically, whereas depression due to inflammatory dysfunction may be a biologically distinct group. In our prior work which was based on a cohort that used depression as an exclusion criteria, we demonstrated that the proteomic profile of AD was more metabolic in nature among Mexican Americans as compared to an inflammatory/vascular driven profile among non-Hispanic whites (O'Bryant *et al.,*2014). The current results suggest the need for a biological stratification of MCI cases for a more comprehensive understanding of underlying causes of cognitive dysfunction. The biological stratification may give providers the tools to know,

which patients may benefit from treatment with an antidepressant to impact cognitive function.

There are several weaknesses worth noting in this study. First, this is an epidemiological study and not a clinic-based study and, therefore, the number of individuals in cognitive dysfunction groups was relatively small and the sample was predominantly female. While the cognitively impaired sample is a reflection of the base rate in the community, a larger more gender equivalent sample would strengthen the study. We are currently conducting a more comprehensive study to include n=1,000 community-dwelling Mexican Americans and n=1,000 non-Hispanic whites, and the current work will be expanded within that cohort. Additionally, the current analyses are cross sectional in nature. However, the ongoing work of the team will capture longitudinal proteomic data for additional analyses to assess change over time. Despite these limitations, this is the first-ever comprehensive examination of diabetes – depression comorbidity proteomic profiles among community-dwelling Mexican Americans. Medical comorbidities impact the proteomic profiles indicative of MCI, which is suggestive of multiple biological dysfunction and can set the stage for additional investigations into the viability of a precision medicine approach to treating and preventing MCI among this underserved population. Additionally, the current findings highlight the need to fully examine medical comorbidities individually and in combination in order to better understand the factors contributing to MCI among Mexican Americans.

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Table 1

Demographics

	Neither (No depression nor diabetes)	Depression only	Diabetes only	Comorbid (depression and diabetes)
Age	N 184 59.77 (7.65)	N 118 60.55 (7.57)	N127 61.68 (8.35)	85 60.02 (6.90)
Gender *%* male	25.0%	21.2%	25.2%	22.4%
Normal Control	159	85	108	62
MCI	25	33	19	23
Years in the US	38.26 (19.04)	34.63 (18.45)	37.85 (19.99)	33.89 (16.32)
Primary Language % English	24.6%	9.84%	19.2%	13.7%
Education in years	8.93 (4.46) 0–18	7.09 (3.88) 0–17	8.05 (4.59) 0–20	7.01 (3.70) 0–17

Table 2

Prediction performance for the impact of comorbid depression-diabetes on the proteomic profile of MCI cases

	Without introducing diabetes and depression		Diabetes only		Depression only		Comorbid (Diabetes And Depression)		Neither (No diabetes or depression)	
Predicted	**MCI**	**NC**	**MCI**	**NC**	**MCI**	**NC**	**MCI**	**NC**	**MCI**	**NC**
MCI	47	0	13	0	23	1	8	0	9	0
NC	39	329	7	87	4	71	10	51	12	119
Precision	100%		100%		95.83%		100%		100%	
Accuracy	90.60%		93.46%		94.95%		85.51%		91.43%	
Sensitivity	.55		.65		.85		.44		.42	
Specificity	1.0		1.0		.99		1.0		1.0	
AUC	.97		.99		.98		.99		1.0	

Table 3

Importance scores for the impact of comorbid depression-diabetes on the proteomic profile of MCI cases

Without introducing diabetes and depression	Diabetes only	Depression only	Comorbid (Diabetes and depression)	Neither (No diabetes or depression)
IL10 23.3	FABP 16.2	TNFalpha 19.9	Eotaxin3 8.0	TNFalpha 9.1
TARC 20.0	IL10 11.8	IL10 11.9	TARC 7.9	B2M 9.0
TNFalpha 19.3	TNFalpha 8.6	IL7 8.2	sVCAM1 7.0	TPO 8.7
FABP 17.4	IL6 6.3	FVII 8.2	TPO 5.6	IL5 7.5
IL5 15.0	TARC 6.1	TNC 7.8	CRP 5.2	IL18 6.8
SAA 14.1	sICAM1 5.8	FABP 7.4	TNFalpha 4.8	sVCAM1 6.2
PPY 12.6	PPY 4.9	TARC 7.2	PPY 4.5	sICAM1 6.2
IL6 12.6	TPO 4.6	IL6 6.7	sICAM1 4.0	FABP 6.1
IL1beta 12.3	Eotaxin3 4.6	SAA 6.0	IL1beta 3.5	IL6 6.0
TPO 12.3	IL1beta 3.9	B2M 5.4	IL5 3.5	PPY 6.0
CRP 10.5	SAA 3.7	TPO 4.3	SAA 3.3	CRP 5.4
TNC 9.8	B2M 3.5	I309 3.7	IL18 2.8	TARC 5.3
B2M 7.5	FVII 3.1	Eotaxin3 3.6	TNC 2.5	Eotaxin3 4.4
Eotaxin3 7.4	IL18 2.7	sVCAM1 2.5	IL6 2.4	IL1beta 3.6
sVCAM1 6.3	I309 2.6	IL1beta 2.4	IL7 2.4	IL10 3.3
IL7 6.0	CRP 2.5	IL18 2.2	B2M 1.7	IL7 2.6
sICAM1 5.9	IL5 1.9	IL5 2.0	FVII 1.7	SAA 2.4
FVII 5.5	TNC 1.4	sICAM1 0.9	IL10 1.3	TNC 2.3
I309 4.8	sVCAM1 1.1	CRP 0.8	I309 0.7	A2M 1.9
IL18 2.0	IL7 0.6	A2M 0.5	FABP 0.1	I309 1.8
A2M 0.6	A2M 0.1	PPY 0.4	A2M 0.1	FVII 0.7