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Levels of α−2 Macroglobulin in cognitively normal Mexican-Americans with Subjective Cognitive Decline: A HABLE Study

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Abstract

Background: The presence of Subjective Cognitive Decline (SCD) in the absence of objective change and the inflammatory biomarker Alpha 2 Macroglobulin (A2M) have both been implicated in preclinical Alzheimer's disease. Mexican Americans are population with high rates of cardiovascular and inflammatory disorders.

Objectives: The current study investigated the levels of A2M in cognitively normal Mexican Americans with and without complaints of cognitive decline.

Method: 293 (243 females, 50 males) community-based cognitively normal older Mexican Americans from the ongoing Health and Aging Brain among Latino Elders (HABLE) study were grouped based on subjective cognitive decline and blood samples were assayed by electrochemiluminescence to determine levels of A2M.

Results: Participants with SCD had significantly higher levels of A2M than those without SCD. Females with SCD had a significantly higher level of A2M.

Conclusions: Results suggest that higher levels of A2M, a marker of neuronal injury, may be involved in subtle changes in cognitive functioning recognizable to persons reporting SCD but too subtle to be objectively measured. Longitudinal research is needed to assess the impact of SDC and A2M in progression to MCI and dementia in Mexican Americans.

Keywords

Alpha 2 Macroglobulin; Subjective Cognitive Decline; Mexican Americans

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Disclosure Statement

SEO has patents and patents pending regarding blood-biomarkers for precision medicine in neurodegenerative diseases and serves on an Advisory Board to Roche Diagnostics. No other authors have conflicts of interest to disclose.

Introduction

In the absence of effective treatments for Alzheimer's disease the field has focused on the identification of preclinical biological and psychosocial markers of the risk for Alzheimer's disease that would allow for the possibility of prevention or early intervention. The pathophysiological processes that eventuate in Alzheimer's disease are widely held to begin many years prior to the appearance of clinically apparent symptoms [1,2]. Among the psychosocial markers that have been investigated is the presence of Subjective Cognitive Decline (SCD) in which individuals perceive themselves as experiencing a decline in cognitive functioning in the absence of objective findings on neuropsychological testing [3,4]. SCD has been shown to be a risk factor for and a very early symptom of later cognitive decline and dementia [5,6]. Although at this point there is insufficient evidence that would indicate that the presence of SCD should be a required component of the definition of prodromal Alzheimer's disease, SCD has been associated with an increased risk for incident cognitive loss over time [7,8]. Cognitively healthy individuals with SCD have been found to have poorer verbal memory [5,9] and show subtle changes in the ability to carry out everyday activities when compared to cognitively healthy individuals without SCD [10].

In addition to psychosocial characteristics such as SCD, a number of biomarkers that would reliably identify individuals in the preclinical stage who are at risk for the development of Alzheimer's have been proposed. These biomarkers include CSF biomarkers, neuroimaging and blood based biomarkers. CSF and neuroimaging have disadvantages as screening tools due invasiveness and cost. A number of blood based biomarkers have been related to the risk for and the progression of Alzheimer's disease [11,12] Alpha 2 Macroglobulin (A2M), an acute phase reactant that is an inflammatory biomarker of neuronal injury that has consistently been found to be associated with Alzheimer's disease [13–17]. A2M has been proposed to be involved in the pathogenesis of preclinical AD [18,19]. A2M has been shown to be related to cerebral amyloid burden in non-demented elderly [18] as well as being related to the progression of MCI [19]. The vast majority of studies done on the role of A2M have been conducted on Caucasians and Asians [20]. and few have included Mexican-Americans, a population at high risk for cardiovascular and inflammatory disorders associated with cognitive decline [21]. The current study investigated differences in the levels of A2M in Mexican-Americans with and without SCD along with possible gender differences.

Materials and Methods

Data from 293 participants (243 females, 50 males) from the Health and Aging Brain among Latino Elders (HABLE) study who had been diagnosed as cognitively normal were analyzed. HABLE is an ongoing epidemiological study of cognitive aging among community-dwelling Mexican Americans that has been described in detail elsewhere [22]. The HABLE protocol collects a wide range of data including health status, clinical laboratory data, affective status, anthropomorphic measures, neuropsychological functioning and proteomic markers. Annually, HABLE participants undergo a medical examination,

clinical interview, neuropsychological assessment, and blood draw for clinical and biomarker analysis. An informant interview is conducted to assess functional level. Data on health habits are collected during the clinical interview. Participants complete measures of depression, anxiety and worry to assess affective distress. In addition, anthropomorphic measures such as height and weight are collected to calculated participant's body mass index.

The neuropsychological test battery is completed in English or Spanish depending on the participant's preference. Of those self-identified as Mexican-American, 67 participants completed the protocol in English and 226 in Spanish. The neuropsychological battery consists of tests of global cognition, executive functioning, language, visuospatial skills, memory and attention. A consensus diagnosis of normal cognition was determined from performance within normal parameters on psychometric testing and a Clinical Dementia Rating (CDR) = 0. The presence of subjective complaints of cognitive decline was determined from the clinical interview. As part of the interview, each participant was asked if they were concerned about changes in memory or thinking. Those responding in the positive were classified as having subjective cognitive decline. Institutional Review Board approval was attained for HABLE and written informed consent was obtained from all participants included in this study in accordance with the ethical standards of the institutional review board and the Helsinki Declaration.

Fasting blood samples were drawn for laboratory analysis. Samples were collected based on a protocol that follows the recently published pre-analytic guidelines [23]. Serum samples were collected in 10-mL tiger-top tubes using 21 g needles, allowed to clot for 30 minutes at room temperature in a vertical position, and centrifuged for 10 minutes at 1,300 x g within 1 hour of collection. Then 1.0-mL aliquots of serum were transferred into cryovial tubes, Freezerworks ™ barcode labels were firmly affixed to each aliquot, and samples placed into 80°C freezer within two hours of collection for storage until used in an assay.

Samples were assayed in duplicate via a multi-plex biomarker assay platform using electrochemiluminescence (ECL) on the QuickPlex SQ 120 imager from Meso Scale Discovery (MSD; http://www.mesoscale.com) per our previously published methods [24]. ECL measures have well-established properties of being more sensitive and requiring less volume than conventional ELISAs, which is the current gold standard for most assays. The markers assayed including Alpha 2-Macroglobulin are from a previously generated and cross-validated Alzheimer's disease algorithm [12].

Cognitively normal participants were categorized into two groups based on interview data--those with complaints of cognitive decline (SCD) and those without (No SCD). Categorical data were analyzed using chi squared; continuous data were analyzed using t-test and ANOVA.

Results

The characteristics of the sample are shown on Table 1. Of the 293 participants with normal cognition, 123 reported having perceived negative cognitive changes and made up the SCD

group and the remaining 170 who denied changes made up the No SCD group. The sample was predominately female and there were disproportionally fewer males in the SCD group. The overall years of education were approximately eight years with no difference found between the groups. The two groups differed in age with the SCD being slightly older. The SCD group ages ranged between 50 and 79 with the ages for the No SCD ranging from 50 to 85. The median age was approximately 60 years for both groups.

Univariate analysis of variance co-varying for age and gender revealed a significant difference between the groups on A2M levels (F=18.109, df=1/289, p=.0001) with a significant difference for age (F=4.279, df=1/289, p=.039). Although there was not an overall significant gender effect, separate analyses were performed comparing A2M levels across gender pairs. No significant difference was found for A2M levels comparing SCD males with No SCD males (t=.2515, df=48, p=.803). However, a significant difference was found between No SCD females and SCD Females (t=4.329, df= 241, p=.0001).

Discussion

Mexican Americans as a group have a high risk for cardiovascular and inflammatory disorders associated with cognitive decline. Our prior work has shown that in a cognitively normal group of Mexican Americans the report of cognitive complaints is related to more affective symptoms, higher levels of diabetic markers and relatively poorer performance on measures of attention and executive functioning [25].The current findings support that levels of A2M, an inflammatory marker of neuronal injury are higher in those individuals who perceive changes occurring in their cognitive functioning in the absence of objective neuropsychological evidence. This suggests that in individuals with SCD, neuronal processes that may eventually lead to cognitive decline and dementia may be ongoing and lead to subtle changes in cognitive functioning that are recognizable to the person but too subtle to be objectively assessed. Our group is studying this cohort longitudinally to assess the impact of SCD and A2M on the progression of cognitive change.

This study has a number of limitations that affect its generalizability. Although the sample is well characterized as cognitively normal, the sample size is relatively small and disproportionally female. The sample is composed of urban dwelling Mexican Americans and the findings may not generalize to other groups. Due to the small number of males the reported gender differences should be interpreted with caution. Even with these limitations the findings do suggest that A2M may be a marker of early changes in the brain potentially related to later cognitive impairment that precede objective cognitive decline.

In older Mexican Americans, a group at high risk for inflammatory disorders, A2M was found to be higher for cognitively normal individuals with subjective cognitive complaints. The findings if supported by longitudinal research suggest that A2M may be useful as a marker of brain changes leading to cognitive impairment in those with subjective cognitive decline.

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Table 1.

Characteristics of the sample.

	SCD N=123	**No SCD N=170**	**p**
Age	*M*=60.054 *SD*=7.059	*M*=58.481 *SD*=6.225	*F=4.279* *p*=.039 *
Education	*M*=8.007 *SD*=4.384	*M*=8.391 *SD*=4.128	*t*=−.849 *p*=.396
Gender % Female	87% Females N= 107 Males N= 16	80% Females N= 136 Males N= 34	χ^2= 2.47 *p*=.116
MMSE	*M*=26.447 *SD*=2.692	*M*=27.077 *SD*=2.346	*t*=−2.030 *p*=.043 *
α−2 Microgloblin	*M*=2171709889 *SD*=4944125753.1	*M*=1936134864 *SD*=503664088.9	*F*=18.109 *p*=.000 *
Males α−2 Macrogloblin	*M*=2106947830 *SD*=448241915 *N*=16	*M*=2068531398 *SD*=527287604 *N*= 34	*t*=.2515 *p*=.8025
Females α−2 Macrogloblin	*M*=2181393935 *SD*=502176505 *N*=107	*M*=1903035731 *SD*=494049487 *N*=136	*t*=4.329 *p*=.0001 *

* *p*>.05