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The Relationships Between Reproductive History, Ethnicity and Alzheimer's Disease Incidence in Women: A Research Protocol

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Abstract

Introduction: In recent years, it has been shown that postmenopausal women have a greater risk of developing Alzheimer's Disease (AD) than their male counterparts. Additionally, greater parity in postmenopausal women is associated with increased AD prevalence. Menopause and childbirth, two factors that affect estrogen levels, are believed to contribute to this health disparity, as estrogen plays an important role in neuroprotection. In addition, few studies have considered the effect of ethnicity on AD incidence in postmenopausal women. It is important to consider the role of ethnicity in the development of effective AD prevention methods for diverse ethnicities. This study seeks to a) investigate the link between increased parity and the development of AD in postmenopausal women of different ethnicities, and b) investigate the effectiveness of estrogen replacement therapy (ERT) in reducing the risk of AD.

Methods: This protocol comprises two studies. Study 1 will include neurological assessment of 200 postmenopausal women to determine AD incidence. These women will be from African, Caucasian, Asian, and Latin ethnicities. The second study will be a randomized, placebo-controlled clinical trial providing ERT to a cohort of 200 menopausal women of the same ethnicities as part A. The treatment will be monitored for AD incidence once every 3 years for 15 years post-intervention.

Results: Based on prior literature, we hypothesize that women of African and Latin ethnicities in Study 1 will have higher AD incidence than Caucasian and Asian women. In Study 2, we expect overall AD incidence to be lower in the ERT group than the control group. We also expect AD incidence to be higher in African and Latino participants than Caucasian and Asian participants post-ERT.

Discussion: The relationship between ethnicity and AD incidence can be confounded by factors such as migratory status and the indirect relationship between racial and genetic groupings. Future studies are required to investigate these factors.

Conclusion: This study will pave the path for further estrogen therapies that can reduce the risk of AD through exogenous estrogen exposure. As AD is prevalent amongst the aging population, findings will also help to reduce health disparities among postmenopausal women of multiple ethnicities.

Keywords: Alzheimer's disease; postmenopause; ethnicity; estrogen; estradiol; parity; reproductive history; dementia; neurodegenerative diseases

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that impairs cognitive ability and primarily affects memory and executive functioning [1]. AD has immense ramifications for the aging population as 1 in 10 people over the age of 65 suffer from AD [2]. AD pathology involves the accumulation of toxic plaques which consist of amyloid-beta (Aβ) peptides and tau protein within specific regions of the brain. When these plaques aggregate in areas of the brain that underlie memory and executive function, cognitive impairment can take place [3]. These toxic plaques have been shown to take several decades to develop. Thus, the clinical diagnosis of AD can occur decades after evidence of Aβ peptides and Tau protein are found within the brain [4].

The frequency of the development of these plaques varies based on sex. In a study conducted in Italy, the incidence of AD was 7.2% in women whereas the incidence in men was 5.3% [5]. In another study, women over 80 years of age had an increased risk of AD relative to men when controlling for age [6]. Estrogen levels are thought to account for the discrepancy in AD prevalence between men and women [7-9]. The effects of Aβ peptides and tau protein block the respiratory pathway within the mitochondria of neurons and lead to neuronal death [7]. When present in normal amounts, estrogenic compounds reverse these toxic effects of Aβ peptides as they bind to estrogen receptors, reactivate the cell signaling pathways within the mitochondria of neurons, and restore normal cell respiration [7]. Estrogen has also been shown to affect neurotransmitters by increasing synaptic plasticity and even

breaking down Aβ precursors [8,9]. In women, endogenous estrogen exposure occurs during their reproductive period, between menarche and menopause. After menopause, there is a dramatic drop in estrogen within the female body, which leaves the brain susceptible to the development of Aβ peptides [10]. However, in men, it is suspected that there are lower rates of AD due to greater levels of circulating testosterone in the central nervous system which can be converted to greater estradiol levels [6]. In contrast to women, testosterone levels in men decline slowly with no drastic drops [8], resulting in a decreased accumulation of Aβ peptides and tau proteins earlier in their lifetime, and thus a lower risk of AD.

Not only are there higher incidence rates of AD in women than men, but studies have also shown an increase in AD risk for postmenopausal women with greater parity [11,12]. During each pregnancy, women are exposed to and maintain estradiol levels more than 10 times the normal menstrual cycle peak for 7 months. It has been shown that these high levels may be associated with greater cognitive decline later in life [13]. Along with a spike of estradiol levels during pregnancy, women who have more children tend to have low circulating estrogen throughout their lifetime, decreasing the neuroprotective characteristics of normal estrogen levels and increasing their likelihood of developing AD [14].

The relationship between increased parity and risk of AD has been thoroughly established and documented in the literature. However, limited research has quantified how the link between parity and AD incidence may differ across ethnicity. Women among different ethnicities may have differing levels of exogenous estrogen exposure due to cultural factors such as lifestyle and diet [15]. Many studies only investigate the epidemiology of the disease within Caucasians, thus limiting the generalizability of their findings from much of the world's population [4]. A study examining AD incidence among different ethnic groups in the United States indicated higher incidence rates in Latinos and Africans in comparison to Caucasians [16]. However, this study was not focused on women and did not take into account differences in parity as this had not been a main area of research.

Additionally, there is still mystery surrounding the benefit of ERT in preventing AD in women. There is an abundance of conflicting literature surrounding whether or not ERT is beneficial or has no effect on the incidence of AD [17-21]. Research suggests that there can be a benefit to using ERT to decrease AD prevalence in women if delivered with the proper methodology such as the use of estradiol treatments [22]. Most studies that were successful in reducing symptoms of AD used estradiol treatments for varying amounts of time and observed improvement in cognitive function for individuals with AD [19-21]. These trials were successful in reducing symptoms of AD, however, they were not able to suggest preventative measures to reduce the risk of AD.

While estradiol supplementation is the most recommended form of ERT, the timing and design of the therapy regimen can greatly influence AD prognosis. Studies have shown that there is a latency period that occurs during menopause where ERT may be more effective at reducing the risk of AD due to the brain's sensitivity to the effects of estrogen [6,11].

This 2 part study seeks to a) investigate AD prevalence between specific ethnic backgrounds in postmenopausal women and b) investigate how ERT therapy can help to prevent AD incidence in women of different ethnicities. As well as assess the correlation of AD incidence with number of childbirths. In study 1, a variety of neuropsychological evaluations alongside an MRI assessment will be used to assess AD incidence in participants. The participants will be 200 postmenopausal women evenly distributed from Caucasian, African, Asian, and Latin ancestry. AD diagnosis will be confirmed by a team of neurologists and neuropsychologists. Study 2 will include a double-blinded, placebo-controlled clinical trial. ERT therapy or placebo will be administered to another cohort of 200 healthy postmenopausal women from the same ethnicities as in the first part of the study. The experimental group will undergo ERT using a 17-beta skin patch for 12 weeks. There will be a post-treatment assessment every 3 years for 15 years in order to compare the incidence of AD post-ERT. This will allow for an investigation into the effectiveness of ERT therapy in the prevention of AD in women. The number of childbirths will be assessed as a continuous variable for correlation analyses throughout both studies.

Methods

Study 1: Epidemiological study of AD incidence in multiparous women of different ethnicities

This is a 2-part study with 2 cohorts of female participants. The first cohort of participants will be 200 women, equally distributed between Asian, Caucasian, Latin, and African ethnicities. Participants will be recruited at multiple testing centers in Canada if they are postmenopausal women between the ages of 60 to 89. Participants must not have a concurrent diagnosis of neurological or psychiatric disorders, traumatic brain injury with loss of consciousness for more than 10 minutes, brain abnormalities as revealed by MRI, vascular dementia or any conditions that may influence cognitive function. In order to determine relative AD incidence within these populations, a Mini-Mental State Exam (MMSE) will be used to determine cognitive function, a California Verbal Learning Test (CVLT) will be administered to assess memory and the Trail Making Test will be used to assess executive functioning alongside an MRI to confirm AD incidence. Confounding variables such as time of day will be controlled. The diagnosis of AD will be confirmed by a panel of neurologists and neuropsychologists. Participants will be asked to disclose the number of childbirths they had within their lifetime to allow for correlational analysis.

Study 2: Estradiol intervention

The second study will consist of a cohort of 200 women of Asian, Caucasian, Latin, and African ethnicities. The participants must be females experiencing natural menopause who are not at risk of obesity, heart disease or breast cancer. A double-blind, randomized clinical trial will include a placebo control group treated over a 12-week period. Each ethnic group will be divided randomly into two groups of 25 women with one group being a control group and the other receiving ERT. The placebo group will receive a placebo patch and the experimental group will receive 0.10 mg/day of estradiol via a 17-beta estradiol skin patch [19-20]. Participants' plasma estradiol levels will be recorded using the 24-hour urine sample method before the therapy is administered and once every 3 weeks thereafter for a 12-week period. After the 12-week treatment period, participants will be assessed every 3 years for a total of 15 years and the MMSE, CVLT and Trail Making Test alongside an MRI will be administered at each visit along with a plasma estradiol check. Data will be analyzed within each ethnic group (placebo versus treatment) as well as cross-analyzed to compare the effectiveness of the ERT in reducing AD incidence between different ethnic groups. Participants will also be asked to disclose the number of children they birthed within their lifetime to allow for correlational analysis.

Results

For study 1, we hypothesize that when we administer the MMSE, CVLT and Trail Making Test alongside an MRI to a group of postmenopausal women of various ethnicities, there will be variability of AD incidence across ethnic populations as shown in previous studies [16,23]. One study conducted over 14 years showed that African Americans have a 2.66% risk of developing AD, with Latin Americans having a 2.22% risk, Caucasians having a 1.93% risk, and finally Asian Americans having the lowest risk of cognitive impairment at 1.52% [23]. However, these studies included both sexes, while our study involves women of varying parity. Thus, we would expect that ethnic groups with greater parity may be at a higher risk of AD incidence.

For study 2, it is expected that there will be a lower incidence of AD amongst the experimental group than the placebo group across all ethnic groups. It has been shown that a normal range of estradiol levels for premenopausal women is 30-400 pg/L and 0-30 pg/L for postmenopausal women [24]. In a study conducted on women who had undergone hormonal therapy for a mean duration of 8.4 ± 2.4 years, the postmenopausal range of estradiol levels increased to 11.1-84.7 pg/L [25]. Thus, we hypothesize that the participants within the experimental group of our study will most likely have estradiol levels between 10-90 pg/L after the estradiol treatment. We also hypothesize that the control group will not have an increase in estradiol levels and will remain within the range of 0-30 pg/L of estradiol after the placebo treatment.

Similar research has shown a decrease in cognitive decline within individuals that undergo estradiol therapy [19-21]. Thus, we hypothesize that those who received ERT in our study will have a general decrease in AD incidence. More specifically, the ethnic groups with a greater incidence of AD such as Africans and Latinos [23] may not have a large decrease in AD incidence because they are more predisposed to developing AD. However, ethnic groups with a lower incidence of AD such as Caucasians and Asians [23] may show a large decrease in AD as the estradiol therapy will boost the lifestyle or genetic factors that are already protecting against Alzheimer's [15].

Discussion

This research proposal consists of 2 studies. In study 1, the incidence of AD in postmenopausal women of Caucasian, African, Asian and Latin ethnicities will be assessed using an MMSE, CVLT and Trail Making Test alongside an MRI. In the second study, a clinical trial will be conducted where a second group of 200 menopausal women will be divided into a control group receiving a placebo patch and a group that receives estradiol therapy as a preventative therapy. They will be observed for a 15-year period to investigate the incidence of AD. Number of childbirths will be assessed to allow for correlational analysis in both studies.

It has been reported that African American and Latin American women have a higher incidence of AD than Caucasian and Asian American individuals [23]. We expect that the AD incidence rates in our cohort of Canadian women will mirror AD rates seen in the United States. Despite this variation within the population in the United States, cross-national studies have shown similar rates of AD incidence in South America and Europe [26-28]. The variation between international and domestic AD prevalence can be attributed to many possible confounding factors.

Migration is a possible confounding factor when evaluating the effects of ethnic background on AD incidence. Migration can be defined as movement across a specific boundary for the purpose of permanent or semi-permanent living. It can occur both internationally and nationally [29]. There has been mixed literature surrounding the effect of migratory status on cognitive function, with most studies associating greater migratory movement with greater cognitive decline [29]. There are many reasons for the possible effect of migration on cognitive decline as migration can have a multitude of effects on lifestyle. Many migrants move from low-income to high-income countries or from rural to urban areas [30,31]. Along with this geographical movement, a more westernized lifestyle often occurs which includes high-calorie diets and sedentary behaviour [32]. This lifestyle can increase chronic disease prevalence such as cardiovascular disease and cognitive impairments [33,34]. Further, those who migrate often experience a great amount of stress [35]

paired with social isolation which can lead to depressive symptoms [36,37]. Depressive symptoms can impact cognition later in life [38]. In our study, we did not take into account the presence of migration within the participants as it is not within the scope of this study. The possible association between migration and AD prevalence can be influential among diverse women in Canada and warrants further exploration.

In addition, one very important limitation to our study is present when discussing the relationship between social and historic racial categories versus genetic and biological ethnic differences. Social and historic racial categories often do not represent the broad spectrum of genetic variability present within them [26]. Further, there are very few genetic differences that have been shown to directly affect health, and most of these differences do not affect all individuals that identify with a certain race, but only a small subset of those individuals [39]. Not only is the distribution of genes within populations inconsistent, but the concept of genotypic versus phenotypic expression is also obscure [40]. Genotype is defined as the underlying genetic makeup of an organism, while phenotype is the expression of these genes which may vary even if individuals possess similar genes. These obscurities suggest that health outcomes are influenced more by social and environmental differences than ethnic factors alone [29]. One environmental factor is the level of formal education within the participants recruited for our protocol. It has been shown that those with higher education have a later onset of clinical AD but quicker rates of cognitive decline after AD onset [41,42].

In the clinical trial of our study, the participants within the experimental group should experience an increase in estrogen levels and have an estradiol level between 10-90 pg/L after the intervention as seen in previous research [25]. In one study, estradiol levels were found to be an accurate predictor of AD incidence within postmenopausal women; participants with estradiol levels less than 20 pg/L had a greater incidence of Alzheimer's [10].

The majority of previously conducted clinical trials utilized conjugated equine estrogen (CEE) instead of estradiol therapy [22,17,18]. Although CEE is very popular, it is composed of a mixture of androgens and estrogens and the function of some of these molecules is unknown as of yet [22]. This can explain why there have been inconsistent results for the effect of estrogen therapy on cognition in previous studies [17-21]. We chose to use the 17-beta estradiol patch as it allows for higher plasma estradiol levels than CEE therapy [22].

While the methods of this study are well-established, there are limitations for this type of intervention which include possible side effects. A previous estrogen therapy clinical trial had to be discontinued due to a significant increase in breast cancer and stroke in participants [7]. The difference between the discontinued trial and ours is that the discontinued study administered 0.625 mg/day of CEE to its participants, which is over six-fold the hormone dose used in our study, explaining the onset of negative side effects. Further, we propose the use of pure 17-beta estradiol therapy instead of CEE which is a mixture of hormones with some unknown functions [22]. Nevertheless, participants from our protocol will be closely monitored for side effects. Other known side effects include weight gain and breast tenderness, with one trial showing that 43% of the women undergoing hormone therapy experienced negative side effects [43]. These side effects could discourage women from choosing to undergo estrogen therapy. Thus, women with a high risk of heart disease, obesity, or breast cancer should be excluded from recruitment as a cautionary measure. Prevention methods for these possible side effects would require further analysis in another dedicated research study.

Conclusions

This research protocol proposes a method to observe AD prevalence within postmenopausal women of various ethnicities as well as a framework for an ERT intervention as a preventative measure to reduce the incidence of AD. As women are disproportionately affected by AD [5,6] and the role of ethnicity in AD incidence has not been thoroughly studied, this protocol could be a stepping stone for eliminating this health disparity among different ethnic cohorts. Further studies should investigate how to maximize the effectiveness of this type of therapy and document possible side effects of ERT. The results of this protocol will contribute to the development and commercialization of new therapies in the prevention of AD in women and assist towards the promotion of healthy aging.

List of Abbreviations Used

AD: Alzheimer's disease
Aβ: amyloid-beta
ERT: estrogen replacement therapy
MMSE: Mini-Mental State Exam
CVLT: California Verbal Learning Test
CEE: conjugated equine estrogen

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

Our study did not require ethics approval or participant consent as it is a research protocol and no new research was conducted with participants.

Authors' Contributions

ZM: made contributions to the design of the study, drafted the manuscript, and gave final approval of the version to be published.
MA: made contributions to the design of the study, drafted the manuscript, and gave final approval of the version to be published.

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