

Ethnic Differences in Early Onset Alzheimer's Disease

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Introduction

In a recent report published by World Health Organisation, it was estimated that there were 46 million people living with dementia around the world and this number is projected to be tripled by 2050 [1]. With the increasing proportion of minorities among elderly populations [2] and a higher prevalence of dementia observed among Hispanics [3-5], Latinos [6] and African Americans [3-6], the burden of dementia in minorities is a challenge for many health systems. Being the most prevalent form of dementia and similar ethnic disparities were reported in Alzheimer's disease (AD) [7], AD should be a priority for countries where populations are composed of a significant proportion of Hispanics and African Americans, like the United States.

Dementia and AD are mostly found in people aged 65 years and over. It can occur in people younger than 65 years and the numbers are alarming [8-10]. This may be due to a growing awareness of early onset dementia in the community as well as an improvement in the diagnostic tools. An accurate estimation of prevalence of early onset dementia/early onset AD, however, is not easy as different diagnostic methods and study designs were used [11]. Nevertheless, it still poses a threat to the health system and society that people with early onset dementia/AD have to face such a challenge at an early age which has a major impact on individuals and families, as well as society compared to those diagnosed at later stage of life [12,13]. The aetiology of younger onset dementia/AD is not fully understood; however, some similarities to the late onset are identified, including ethnic disparities between whites and other minorities [3]. Our studies suggested that native Americans, Alaskans and African Americans were at greater risk of developing early onset AD than other ethnicities [14].

Explanations for such ethnic disparities may be grouped into genetic factors, family history, socio-economic status and comorbidities associated with cerebrovascular dysfunction. It should be noted that most results are potentially biased due to small sample size, poor study design or possible misclassification of ethnicity. Studies illustrate that among younger onset dementia patients such assignment of ethnicity may be incorrect or uncertain in 30-50% [15]. The cultural and linguistic backgrounds of minorities may further reduce the accuracy of cognitive and behavioural assessments. These limitations should be borne in mind when interpreting findings.

We summarise the findings that explore the pathways between ethnicity and AD. Some studies suggest differences could be cultural—that is, some cultures perceive dementia-related symptoms as part of the aging process [16-20], which is beyond the scope of this review.

Factors Relating Ethnicity to Alzheimer's Disease

Genetic factors

Research exploring genetic effects in AD has increased our understanding of patho-mechanisms. Genetic background contributes to the higher incidence of dementia in certain minority groups [5,21-23]. One of the well-known genes is Apolipoprotein E (APOE). It is a major cholesterol carrier that supports lipid transport and has a role in

injury and repair in the brain. There are three major forms of APOE— $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. APOE $\epsilon 4$ alleles increase risk for AD and cerebral amyloid angiopathy [24].

The APOE $\epsilon 4$ allele effect is evident at all ages between 40 and 90, but less marked after age 70; the presence of APOE $\epsilon 2/\epsilon 3$ alleles appear to have a protective effect and similar across different ethnicities [22]. Nevertheless, there are some ethnic differences identified. Farrer et al. found that, compared with those who did not have APOE $\epsilon 4$, white and Hispanic people who inherited APOE $\epsilon 4$ from one of the parents were at a greater risk of developing AD (in comparison to African Americans) [22]. For people who inherited an APOE $\epsilon 4$ allele from parents, whites and African Americans had higher risks of developing AD. Notably, the association between APOE $\epsilon 4$ and AD that is found among minorities is weaker than the association with whites. Nevertheless, this weaker association explains, in part, the greater prevalence of AD and other dementias in African Americans and Hispanics. Another study found that with one or more APOE $\epsilon 4$ allele, African American and Hispanics were more likely to develop AD, controlling for years of education [25].

Most studies suggest that African Americans and Hispanics have a greater risk of developing AD when an APOE $\epsilon 4$ allele is present. This increased risk cannot be explained by an effect of the APOE $\epsilon 4$ allele alone, proposing that some other factors are operational. Some studies indicate that the APOE genotype is related to ancestry; the high-risk allele among African Americans could be gradually attenuated as a result of mixture with other ethnicities or modified by environmental factors [26,27].

Family history

The association between family history of dementia and the risk of developing AD has been established [28-30], and authors have suggested that the effect is only present among people who carry APOE $\epsilon 4$ [31]. Studies examining the impact of family history on dementia are often biased, as the effect could be easily masked by genetic factors or other risk factors [29]. In the study by Green et al., there is evidence to suggest that, after stratifying for APOE genotypes, females with a family history were at a greater risk of developing dementia than males among whites [29]. A similar effect was found in African Americans; increased risks were also found in spouses as well as first degree relatives. These authors concluded that family history has a similar effect among whites and African Americans and ethnicity has a stronger effect than family history. However, self-reported ethnicity and lack of control for

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educational level may have contributed to the observed risks in these studies. A recent study found a family history of dementia increased the risk of AD and the risk is independent of the APOE $\epsilon 4$ allele [32]. Devi et al. observed a similar pattern among Hispanics; having relatives with AD provided an increased risk of AD compared to controls [33]. This increased risk was also found among whites but not among African Americans. Two studies suggest that this association is more obvious with female relatives [29,33].

Familial AD can be inherited through gene mutations; and these forms are more common in younger onset dementia [34]. Early-onset familial AD, which typically develops before the age of 65 years and accounts for only a small portion (<1%) of AD cases, is primarily caused by overproduction of A β owing to mutations in either the APP gene or genes encoding presenilin 1 (PSEN1) or presenilin 2 (PSEN2), essential components of the γ -secretase complexes responsible for cleavage and release of A β [23,35,36]. No relationship between ethnicities and these gene mutations has been observed.

Socioeconomic status (SES)

Many studies use ethnicity as a surrogate of SES—there is a strong relationship between low SES in African Americans and Latinos/Hispanics with the development of dementia [37-41]. A similar association is observed in measures of social integration, such as parental or early life socioeconomic position, childhood IQ, educational attainment, occupational characteristics, cognitive function and neurocognitive disorders [42,43]. Ethnic disparities and the risk of developing AD must consider the effect of SES. However, an examination of multiple prospective cohorts which investigated the role of cognitive performance, memory and executive function at baseline and over time found there were differences by race/ethnicity at baseline (whites higher than minorities); this pattern did not hold for cognitive decline after adjusting for years of education [44]. The effects of education and ethnicity were not consistent between studies.

The possible explanations for lower cognitive test scores for Blacks and Hispanics include the bias of the tests or the different types of tests [45-48] and lower levels of SES [49-51]. This is particularly so with lower levels of educational attainment and the quality of education, which might explain the substantial variation in cognitive test scores among ethnicities [52-54]. It is clear that early life experiences, particularly education, have a great impact on cognitive test scores in later life. Therefore, it is important to consider education and SES when assessing ethnic disparities in AD.

Comorbidities

Conditions like stroke, diabetes, hypertension, congestive heart failure, high fat intake, high cholesterol, smoking, alcohol misuse, atrial fibrillation, low folate and obesity were found to be associated with cognitive decline and dementia [42]. Other studies have confirmed the relationship between hypertension, heart disease, diabetes, stroke and AD [55-62]. Our study confirmed that hypertension is a risk factor for early onset AD [63]. Similar to SES, people with multiple conditions/diseases, the risk of developing AD and other dementias is increased [64]. The Health and Retirement Study [39] found that in those people with cognitive impairment, the proportion of individuals with high blood pressure was higher than those without cognitive impairment for African Americans, Hispanics and non-Hispanic whites. The same relationship was observed for diabetes, stroke and heart disease. Nevertheless, high blood pressure and stroke were more common among African Americans, but diabetes was more common in both

African Americans and Hispanics compared with whites. Hispanics seem to have less heart disease compared with the other two ethnicities.

Purnell et al. reviewed published works that examined the effect of cardiovascular risk factors on the risk of AD [65]. Although most studies reported a significant association between hypertension and AD, the definition of hypertension is not consistent nor follows generally accepted clinical criteria. If strict criteria were adopted, then future studies might shed light on this association.

The relationship between diabetes and AD risk was similar to hypertension; most studies did not observe a significant relationship and for those that did, diabetes often interacted with other factors, particularly hypertension [65]. A recent study reviewed cohort studies and pooled results to examine the relationship between diabetes and AD. They found that diabetes was associated with a higher risk of AD; however, this association was observed in both Western and Eastern populations—Eastern populations having higher risk [66]. This study did not examine other ethnic differences.

Cholesterol levels have also been investigated; however, the findings are less conclusive most studies have shown that high cholesterol levels increase the risk of AD; some did not. One study found the risk was reduced for people with a high level of cholesterol [67]. There is some evidence to suggest that high cholesterol levels may have variable impacts in different ethnic groups [68].

Again, most studies did not reveal a significant association between stroke and AD. A significant association was only observed when stroke interacted with other diseases variables [58].

Based on these findings, it seems that the relationship between the above comorbidities and the risk of AD are not conclusive. Nevertheless, it is believed that these conditions account for some of the ethnic differences in the prevalence of AD and dementia. For example, one study found that reducing ethnic and racial disparities in the incidence of Type 2 diabetes could reduce the incidence of cognitive impairment and dementia by 17% [69]. Studies in the 1990s found that the high prevalence of cerebrovascular diseases amongst African Americans and Hispanics probably explains the higher incidence of vascular cognitive impairment [70-72].

Conclusion

It is clear that most observational studies identified a greater risk of AD in African Americans and Hispanics compared with the non-Hispanic white population. The possible explanations are that these minorities have a high prevalence of at-risk genes that lead to dementia, low socioeconomic status associated with low or poor-quality education, and high prevalence of comorbidities—hypertension, diabetes, stroke and heart disease. Studies generally support one of these factors as operational for ethnic differences in dementia and most studies agree on the different prevalence of APOE $\epsilon 4$ among ethnic groups. Nevertheless, we posit that none of these factors alone can explain the excess risk of AD among African Americans and Hispanics compared to whites. To further elucidate these ethnic disparities requires prospective analyses of large cohorts of African Americans and Hispanics to tease out the effects of each risk factor and its mechanism of action in each ethnic group. Such a study will increase our understanding of the patho-mechanisms of AD in general.

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