

Intercontinental Epidemiology of Alzheimer Disease

A Global Approach to Bad Gene Hunting

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THE POPULATION OF AFRICAN AMERICANS OLDER THAN 65 years and therefore at risk for Alzheimer disease (AD) and other dementias is increasing even faster than the white population in this age group.^{1,2} In general, studies have found rates of dementia in African Americans to be comparable with or higher than in whites.³⁻⁵ However, this issue is far from clear. Vascular dementia (VaD), which is more prevalent among African Americans than whites,⁶ is usually attributed to the higher prevalence of cardiovascular risk factors. For example, according to data from the Third National Health and Nutrition Examination Survey from 1988-1991, 24% of the US population has hypertension.⁷ The age-adjusted national prevalence is higher in non-Hispanic African Americans (32.4%) overall, and even higher for African Americans in the southeast region of the country: 35% for African American men, 37.7% for African American women.⁸ The definitive diagnosis of VaD is more imprecise than that of AD, and the prevalence of mixed dementias (AD and VaD) is more elusive,⁹ even with the advent of more precise clinical criteria.⁹⁻¹¹

Whereas the familial risk of AD appears similar in African Americans and whites,¹² the specific factors conferring genetic susceptibility and their mode of action may differ between these groups. The most widely accepted factor identified to date is the $\epsilon 4$ allele of apolipoprotein E (APOE), increasing the risk among whites between 2.7 and 3.2 in persons having a single allele and between 12.5 and 14.9 in those homozygous for this factor.¹³ The $\epsilon 4$ association is also evident in the Japanese population.¹³ In contrast, studies in 2 community-based cohorts of African Americans suggest that the $\epsilon 4$ effect is significant but much weaker in $\epsilon 4$ homozygotes, and absent altogether in $\epsilon 4$ heterozygotes.^{14,15} The reasons for ethnic differences in the $\epsilon 4$ effect are unclear.

Cross-cultural studies provide an opportunity to elucidate modifiable risk factors for dementia. Unfortunately, results from most studies of this sort are often difficult to

interpret because of genetic and environmental differences between populations. For example, in most studies the prevalence of VaD is higher in Japanese than European populations.¹⁶⁻¹⁸ In part due to the higher rates of stroke in Japan, differences in methods of ascertainment limit cross-cultural comparisons of absolute prevalence rates. Comparing the ratio of AD to VaD is also informative. In Western nations, the prevalence rate of moderate-to-severe dementia among those older than 65 years is 4.6% (AD:VaD, 1.7). In Japan, the prevalence rate of dementia is similar (4.5%) but the ratio is reversed (AD:VaD, 0.5).^{17,18} In the Ni-Hon Sea study,¹⁹ methods for case ascertainment were standardized in Japan, Hawaii,²⁰ and Washington State.¹⁶ As persons from Japan immigrated to Hawaii and then to the US mainland, the ratio of AD to VaD changed progressively from an Asian to a Western pattern: 0.55 for Japan; 0.67, Hawaii; and 2.0, Washington. The shift across 3 genetically related, but culturally diverse, groups suggests a dynamic interaction between genes and environment.

Population-based studies of dementia currently under way in Ibadan, Nigeria, and the Nyeri district in Kenya may lead to a better understanding of risk factors for AD in African Americans. Results have already started to emerge from the Indianapolis-Ibadan Dementia Project. The age-adjusted prevalence rates of AD and dementia are significantly lower in Yoruba from Ibadan than in community-dwelling African Americans living in Indianapolis,²¹ but these rates may reflect differences in life expectancy or survival after onset of the disease rather than differences in disease susceptibility. In this issue of THE JOURNAL, Hendrie and colleagues²² provide a better estimate of disease rates in these 2 areas. Based on findings from their community-based, 5-year prospective follow-up of individuals cognitively intact at baseline, the authors report age-standardized annual incidence rates for both dementia and AD that are 2 to 3 times lower for Yoruba than for African Americans. These findings, especially if confirmed in Nyeri or other African popula-

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tions, favor the idea that environmental or cultural factors, in concert with genetic predisposition, strongly influence susceptibility to AD.

By studying incidence of disease, Hendrie et al were able to minimize the impact of the inevitable biases embedded in studies comparing participants from developed and nondeveloped countries. These researchers invested substantial time and energy to establish an infrastructure for conducting a sophisticated epidemiological research study and to develop standardized screening instruments for use in culturally disparate, nonliterate, or literate populations.^{23,24} However, there are 2 unresolved questions. First, despite the extraordinary measures taken by the investigators, are there additional sources of bias that could account for these striking differences in incidence? Second, if the differences in incidence are real, what is the cause and what are the implications of these differences for our understanding of AD?

The raw data of the study reveal the striking differences between the 2 populations: the higher mortality rates among the Yoruba participants and the higher refusal and lost-to-follow-up rates among the African Americans. The authors adjusted for these differences in estimating the incidence rates, but these factors could confound results in ways that adjustment does not remedy entirely. If persons with incipient dementia are disproportionately represented among the early deaths in Ibadan, then they would be censored from the pool of surviving participants, resulting in a lower observed incidence.

The potential confounding due to differential refusals and drop-outs also may be problematic if they are unevenly distributed. It is possible that elderly African Americans who have not sought medical attention and may not be inclined to participate in medical research are less likely to participate in longitudinal research. If so, and if those individuals were more likely to have incipient dementia, then the incidence rates among the Indianapolis cohort might be an *underestimate*. On the other hand, if investigators made extra efforts to retain those African Americans who seemed to be on the edge of poor performance, then the refusals and drop-outs might come disproportionately from healthy participants, leaving a pool of subjects enriched for incipient dementia.

If these estimates are accurate, what might they imply? The obvious conclusion is that different genetic factors may mitigate vulnerability to AD. Although most non-Caribbean African Americans trace their ancestry to western and central Africa (ie, the region including Ibadan),²⁵ admixture with other racial backgrounds may have increased the frequency of AD susceptibility alleles that are rarer or even absent in black Africans. However, this explanation is not supported by evidence showing comparable frequencies of the APOE $\epsilon 4$ allele in Indianapolis, Nigeria, Tanzania, and Kenya.^{15,26-28} Notably, the AD/ $\epsilon 4$ association is not significant in Yoruba or Tanzanians,^{15,28} whereas $\epsilon 4$

homozygosity is significantly associated with AD risk in African Americans,¹⁴ albeit much less so than in whites.¹³ It is possible that other risk-enhancing or protective genetic factors may account for some of the differences in incidence rates between the populations, and the search for such factors is currently a major research focus.

Another likely explanation is the effects of environmental factors, such as diet and exercise, on risk of dementia. Preliminary evidence suggests that a high-fat diet may increase the risk of developing AD.²⁹ Transgenic mice prone to developing AD pathology and fed a hypercholesterolemic diet produced significantly higher levels of amyloid- β peptide, suggesting alterations in amyloid precursor protein processing in response to high cholesterol.³⁰ Cross-sectional studies have revealed that AD cases are less active physically than controls in early life (20 to 60 years).³¹ Physical activity is correlated with cardiovascular health perhaps by influencing blood pressure and cholesterol level. These lifestyle factors may be surrogate markers for cerebrovascular disease. Cerebrovascular disease and AD pathology frequently coexist.³² Evolving epidemiologic evidence suggests that the presence of risk factors for stroke is associated with an increase in incident dementia.³³ Several studies identify atherosclerosis and hypertension as risk factors for both VaD and AD.^{34,35} This suggests that vascular disease may contribute to AD pathogenesis or may accelerate the clinical presentation of AD. The influence of stroke risk factors and coincident cerebrovascular disease on incident dementia also may vary by ethnic background,^{35,36} as suggested by studies of US African American,³⁶ Hispanic,³⁷ and Japanese persons.³⁸ In light of the recognition by Hendrie et al of the lower prevalence of vascular risk factors in Yoruba compared with African Americans, it would be enlightening to know the frequency of cerebrovascular risk factors and events among subjects who died or were lost to follow-up as well as among the survivors with and without dementia in the Indianapolis and Ibadan populations.

If modifiable factors such as diet were found conclusively to modulate the risk of AD to the degree suggested by this research, then we would all indeed rejoice at the implications. And in the seemingly endless tug-of-war between genetic and nongenetic influences in disease, new emphasis will emerge not only on the environmental factors, but also on the complex interactions between genetic predisposition and environmental triggers.^{39,40} While this research is only 1 step and the first of many needed to establish such a connection, the possibility that unique genetic and environmental risk factor profiles could be established could substantially alter our current understanding of AD. If such profiles could be established, cognitive enhancing treatments might be tailored to a particular risk group.

Regardless of the implications of this study for understanding racial and cultural risk of dementia, this remark-

able study moves medical science another step forward in exploring the etiology and risk factors of this highly prevalent and devastating disease.

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