Exploration of Environmental and Genetic Risk Factors for Alzheimer's Disease: The Value of Cross-Cultural Studies

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Abstract

Advances in molecular genetics have revolutionized epidemiological research. It is now possible to combine the techniques of population genetics with research on risk factors to construct genetic-environmental interactive models that explain geographic-ethnic variations in disease rates. Cross-cultural studies involving populations from developing and developed countries offer a unique opportunity for constructing these models by providing a wide diversity of environmental exposures. Results from a comparative Indianapolis-Ibadan study suggest that Alzheimer's disease incidence rates are lower in Yoruba than in African Americans and that these lower rates may be due to a combination of genetic and environmental, primarily dietary, influences.

Keywords

Alzheimer's disease; cross-cultural; genetics

Advances in molecular genetics have revolutionized epidemiological research. Vague, ambiguous concepts such as race and ethnicity need no longer be considered as risk factors. Instead, epidemiologists are now able to combine the techniques of population genetics with more traditional research on risk factors to formulate etiological hypotheses involving specific genes and specific environmental factors that can explain geographic or ethnic variations in disease rates.

Cooper and Kaufman (1998) recently proposed a disease model involving contributions from genes and the environment to explain disease rates in populations. They emphasized that genetics and the environment interact in such a way that the presence of the two factors does not always imply that their influence amounts to the sum of the two effects (see Fig. 1). The propensity to develop an illness does not depend solely on the presence or absence of a specific gene mutation or variant. Rather, it depends on the biological products of that gene (gene expression), which can be influenced by environmental as well as other factors.

Cross-cultural studies of Alzheimer's disease (AD), particularly those involving subjects in developing countries, offer a unique opportunity for applying this proposed disease model to AD because such studies provide a much wider diversity of environmental exposures than do studies of populations solely in industrialized countries, where important risk factors may be missed because of their very pervasiveness. The environmental diversity cross-cultural studies bring into play makes it possible not only to identify new environmental factors, but also to explore the effect of this environmental diversity on gene expression. Since 1992, research teams from the Indiana University School of Medicine and the University of Ibadan, Nigeria, have been collaborating on a longitudinal comparative study of the prevalence and incidence rates of AD and other dementing illnesses and their associated risk factors. Our study's participants, who are all age 65 years and older, include African Americans residing in Indianapolis and Yoruba living in the Idikan wards of Ibadan, Nigeria. In this review, I discuss how Cooper and Kaufman's model might be applied to cross-cultural research in AD using data primarily from this Indianapolis-Ibadan project. The major methodological problems that exist with respect to cross-cultural research are not discussed.

$$\text{Observed Phenotypic Variation} = \text{Genes} + \text{Environment} + \text{Genes} * \text{Environment} + \text{Genes} * \text{Genes} + \text{Environment} * \text{Environment}$$

Fig. 1. Modeling the contribution of genes and the environment. Asterisks indicate interaction between factors (from Cooper & Kaufman, 1998, p. 815).

COMPARISON OF RATES OF AD BETWEEN POPULATIONS

Many studies have been conducted on the prevalence of AD throughout the world, but few have been conducted in nonindustrial countries and fewer still have used the same methodologies used in studies of industrial countries (Hendrie, 1998). We have reported significantly lower rates of dementia (8.24% vs. 2.29%) and of AD (6.24% vs. 1.41%) in Yoruba than in African Americans. Our prevalence rates for African Americans are approximately the same as those reported in the large cross-Canada national prevalence study. Our prevalence rates for Yoruba are at the lower end of previously reported rates.

Prevalence rates, however, depend on factors in addition to incidence rates of illness. Differences in life expectancy or in survival of demented and nondemented subjects between sites could also affect prevalence rates. Incidence rates, which are the numbers of new cases occurring over a fixed period of time, are a better indication of true rates of illness than prevalence rates. In our 5-year incidence study, the age-standardized incidence rates for both dementia and AD were significantly lower for Yoruba than for African Americans (for dementia: Yoruba, 1.35%, and African Americans, 3.24%; for AD: Yoruba, 1.15%, and African Americans, 2.52%; Hendrie et al., in press). It should be noted that although prevalence and incidence rates were consistently lower among the Yoruba, the association with age was identical between sites; that is, prevalence rates in both sites roughly doubled every 5 additional years of age.

COMPARISON OF FREQUENCY OF PUTATIVE RISK FACTORS BETWEEN POPULATIONS

Great cultural and socioeconomic differences exist between the impoverished, predominantly Muslim residents of the Idikan wards of Ibadan and the elderly African Americans living in Indianapolis. The elderly Yoruba have relatively limited access to health care and live, for the most part, in large extended families. In contrast, most of the African Americans in our study reported good access to health care and either live in single-family dwellings with members of their immediate family or are widowed and live alone. Many studies report a high level of education as a protective factor against the development of AD. In Ibadan, more than 80% of the subjects had received no education. In Indianapolis, the mean number of years of education for our cohort was 9.6. This finding is counterintuitive in view of the low rates of AD in the Yoruba. It might suggest that education level is not directly related to AD risk but instead serves as a marker for other influences in childhood. In the African Americans, for example, it was the combination of low education and childhood residence in the rural South that increased the risk of AD (Hall, Gao, Unverzagt, & Hendrie, 2000).

There are many lifestyle differences between the two populations in our study. For example, dietary intake varies widely: The elderly Yoruba in the Idikan wards consume a low-calorie, low-fat diet consisting mainly of grains, roots, and tubers, supplemented with a small amount of fish. Ascorbic acid levels have been reported to be relatively high among the Yoruba, probably because of the high consumption of peppers. The African-American diet, however, is high in fat and sodium and low in fiber. These lifestyle differences are reflected in significant differences in biological and medical variables (see Table 1) that are often associated with risk of circulatory problems such as heart attack and stroke.

There is mounting evidence that not only is vascular disease associated with stroke-related dementias, but it may contribute to the development and progression of AD as well. The relatively lower incidence of vascular disease and vascular risk factors in the Yoruba than in the African Americans may account for the differences in rates of AD and dementia between the two sites. As our study is longitudinal in design, and enables us to conduct predictive analyses on the effects of these risk factors, we hope to test this hypothesis. It is also possible that the interaction of these vascular risk factors with other genetic risk factors may account for the differences between the two populations.

Table 1. *Summary of biological and medical variables that are significantly different between Yoruba and African-American subjects*

Variable	Yoruba (*n*)	African Americans (*n*)
History of hypertension	19% (2,470)	61% (2,204)
History of diabetes	2.5% (2,482)	24% (2,206)
History of stroke	1.3% (2,480)	11% (1,960)
Ever smoked	24% (2,472)	63% (2,205)
Mean cholesterol (mgs/dl)	166 (71)	221 (117)
Mean body mass index	21.4 (1,104)	28.9 (1,115)
Mean systolic blood pressure	135 (1,213)	146 (945)

GENETIC RISK FACTORS

Early-onset inherited forms of AD have been associated with gene mutations on three chromosomes, 21, 14, and 1. These findings are extremely important for understanding the pathophysiological mechanisms of AD but account for only a very small proportion of all Alzheimer's cases (about 2%).

Apolipoprotein ε (ApoE), a fat-bound protein circulating in the blood, is known to play an integral role in cholesterol transport. This protein exists in several slightly different structures with similar function; these three *isoforms* are encoded by separate forms (alleles) of a gene on Chromosome 19. The three alleles are termed ε2, ε3, and ε4. Inheritance of these alleles is similar to that of blood groups (i.e., everyone inherits two alleles, one from each parent). The ε4 allele has now been identified as an important risk factor for the most common forms of late-onset AD; specifically, individuals possessing two copies of this allele have a greater risk for AD (up to eightfold or more) than do individuals with no copies, and individuals with a single copy have an intermediate risk (2 to 4 times that of individuals with no copies).

The association between ApoE ε4 and AD is one of the most consistent findings in AD research, being confirmed in many studies throughout the world. One of the intriguing features of the studies conducted so far is the marked variation in frequency of the ApoE ε4 allele found in different population and ethnic groups. Reported frequencies of the ε4 allele have ranged from 5% or less in the Amish to more than 40% in some Aboriginal populations. It is not clear yet what effect this variation in population frequency has on the rates of AD in these populations.

In our Indianapolis-Ibadan study, the frequencies of the ApoE alleles were almost identical in the two populations (Indianapolis: ε2–10%, ε3–68%, ε4–22%; Ibadan: ε2–8%, ε3–71%, ε4–21%). In contrast to previous studies of Caucasian and other population groups, our study showed only a weak association between ε4 and AD in African Americans; this association attained significance only for those individuals who possessed two copies of the ε4 allele. In the Yoruba, so far we have found no association between ε4 and AD for individuals with either single or double copies of ε4.

POSSIBLE GENETIC-ENVIRONMENTAL INTERACTIONS

The lack of association between ε4 and AD in the Yoruba may explain in part some of the difference in rates of AD between the Yoruba and the African Americans. It may be that there are differences between the two populations in other genes that regulate the expression of AD. We are currently exploring this possibility.

The differences in cholesterol levels between sites and the role that ApoE plays in cholesterol processing make an ApoE-cholesterol interaction resulting in a differential AD risk an obvious possibility. Two prior studies have reported a significant interaction between ApoE and cholesterol in determining risk for AD (Jarvik et al., 1995; Notkola et al., 1998). Notkola et al. (1998) suggested that cholesterol, in fact, mediates some of the effects of ApoE ε4 on AD. In a preliminary study, increasing levels of cholesterol increased the risk of AD in African Americans, but only in those subjects who did not possess an ε4 allele (Evans et al., 2000). The relationship was not seen in the Yoruba, perhaps because they had much lower levels of cholesterol. It is too early to tell whether or not this mechanism accounts for the different rates between the two sites.

Cell functioning is dependent on the metabolism of oxygen. However, this metabolic process throughout life can create toxic by-products, which can eventually cause cell death. This potentially cell-destroying process is referred to by the term *oxidative stress*. As one of the most metabolically active organs, the brain is particularly vulnerable to oxidative stress. Low-calorie diets produce less evidence of oxidative stress than high-calorie diets; oxidative stress also appears to be reduced by diets containing high levels of antioxidants (e.g., vitamins C and E), which act as scavengers for the toxic oxidative end products. It might be anticipated, therefore, that the diet of the Yoruba would produce less evidence of cell damage due to oxidative stress than would the diet of African Americans. In fact, in a very small study involving cells from 8 Yoruba subjects (5 with probable

AD and 3 normal subjects), there was little evidence of oxidative stress (probably because of diet), which might explain at least in part the lower incidence rates of AD in Yoruba (Lahiri et al., 1999).

Both of these preliminary studies suggest that diet or dietary products may be a mediating influence on the association between ApoE ε4 and AD. Again, it must be emphasized that these results are only very preliminary and will need confirmation in our longitudinal studies. Moreover, it is likely that ApoE ε4 will not be the only genetic factor that confers risk for AD. Already there is evidence to suggest that a gene located in Chromosome 12 may be implicated in AD. Many other possible interactions that may alter the association of ε4 with AD have yet to be explored.

Also, we have as yet studied only the Yoruba. It is entirely possible that other African groups would show different gene-environment associations with AD. There is at least as great a genetic diversity among Africans as among non-Africans. The variation in frequencies of ε4 is at least as great within African populations as across populations around the world.

CONCLUSION

The contrast between the advances in the understanding of the role of genetics in AD and the inability to identify environmental factors clearly, together with the lack of clear evidence of differences in incidence rates between countries, has led many investigators to speculate that AD is predominantly or exclusively genetic in origin. Cross-cultural transnational research, by providing greater environmental diversity, offers the opportunity to identify hitherto unsuspected environmental influences and interactions between environmental and genetic factors that may alter gene expression. Cross-cultural studies such as ours are still in their infancy. So far, we have established two populations with different incidence rates of AD and have identified some potential environmental risk factors. Our next major step is to assess the association of these risk factors (using more accurate biological measurements of them) to AD in both populations and to explore how they may interact with genes in a longitudinal study. We hope to establish a disease model that will account for differences in AD incidence in both populations.

By the year 2005, about 70% of all elderly worldwide will be living in developing countries. If the prevalence rates of AD in developing countries in any way parallel the rates in developed countries, the burden of caring for these AD patients in these countries will be staggering. We hope that by including two populations, one from the developing world and one from the developed world, our model for AD will be more generalizable than models constructed primarily from populations in Western societies.

Recommended Reading

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Note

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