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Perspective on Race and Ethnicity in Alzheimer's Disease Research

Myron F. Weiner, M.D.

Departments of Psychiatry and Neurology, University of Texas Southwestern Medical Center

Abstract

There are adequate scientific, public health and ethical justifications for studying Alzheimer disease (AD) in persons of varying race and ethnicity, but to be meaningful variables, race and ethnicity must be examined in context. The complex interactions between race, ethnicity, life style, and environmental factors such as climate and diet, require that future studies of AD in specific racial or ethnic groups attend to measures of racial/ethnic homogeneity and assessment of the environment and the elements that comprise the ethnicity of groups under study. Instead of arbitrarily selecting specific racial or ethnic groups in the hope of finding important differences, it may be in the long run less costly and more efficient to recruit families with highly positive (or negative) family histories, to search within these groups for possible racial or ethnic differences and to then investigate the possible racial or ethnic reasons for those differences.

This perspective is offered by a clinician/researcher with 16 years of experience working in Oklahoma and Texas with American Indian dementia patients and their families. This work has been made possible by NIA funding of an American Indian Satellite awarded to the Alzheimer's Disease Center at the University of Texas Southwestern Medical Center and by the cooperation of the Cherokee Nation, The Dallas Urban Intertribal Center, and the Choctaw Nation.

A proper beginning for this perspective on studying Alzheimer's disease (AD) in persons of different racial and ethnic groups is to establish working definitions of race and ethnicity, recognizing that no sharp genetic boundaries can be drawn between human population groups (Bonham et al., 2005). Race can be seen as a fixed characteristic of a person, linked to genetic heritage. Ethnicity is a broader construct including culture, history, language, religion, and often, shared genetic heritage (Burchard et al., 2005). Stated another way, race is largely genetically determined; ethnicity is largely self- or group-defined. It is therefore possible for persons of different race to be of the same ethnicity and persons of different ethnicity to be of the same race. Population genetics suggest the existence of 5 races: African, Caucasian, Pacific Islander, East Asian, Native American, and admixtures thereof, all having their origin in the African continent (Howells, 1992); the U.S. Census lumps Asians with Pacific Islanders (U.S. Bureau of the Census, 1994). By contrast, the potential number of ethnicities is as large as the number of clusters of human beings, who by proximity and common life experiences develop and share an overarching belief system and a set of customs and rituals that enforce their belief system. And like race, ethnicity, once established, is not bound to a geographical location.

Myron F. Weiner, M.D. 5323 Harry Hines Blvd, Dallas, TX 75390-9129, Telephone: 214-648-9353, fax 214-648-2031, email: myron.weiner@utsouthwestern.edu.

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In their introduction to a series of papers commissioned by the Alzheimer's Association on the interaction between culture (e.g., race and ethnicity) and AD, Radebaugh and Ward-Robinson (2002) point out that because human beings are 99.9% genetically identical, our differences must stem from experiences and environments across the lifespan. This fits AD very well. Even in monozygotic twins, the concordance of AD is only 60%, and when both twins are affected, there may be as much as 7 years difference in disease onset (Gatz et al., 2005). Radebaugh and Ward-Robinson agree with Risch et al. (2002) that loose categorizations of individuals for research or clinical purposes may actually conceal more information than they reveal, and that within-group heterogeneity may be even greater than the differences between racial and ethnic groups. This caveat is supported by observations of Choctaw Indians in southeastern Oklahoma. Within the 10 ½ rural counties encompassed by the Choctaw Nation are small groups of Choctaw full-bloods living in relative isolation, speaking Choctaw, adhering to Indian religious beliefs, lacking amenities such as telephones and televisions, and making little use of Western medicine. On the other hand, the average Choctaw elder who presents for dementia evaluation at the Choctaw Nation Healthcare Center and its satellite clinics has only 25% Choctaw heritage, speaks only English, has 11 years of education, belongs to a Protestant denomination, and possesses a television and frequently, both conventional and cellular telephones. Thus, isolated full-bloods may have more in common with recent non-English-speaking immigrants to this country than with their Americanized fellow Choctaws. It appears, then, that to be maximally useful, racial and ethnic categorizations must also include information such as primary language, literacy, acculturation, ability to meet needs for clothing, shelter, etc., and place of residence (such as rural, inner city, etc.).

Radebaugh and Ward-Robinson further suggest that through designing and conducting epidemiologic studies, investigators may learn enough about various subcultures (within the same race or in different races) to enable effective recruitment and retention of research subjects, to develop assessment instruments valid for each subculture, to develop culturally competent health care professionals, and to educate caregivers. A major problem with this approach is that every race and ethnic group contains numerous subcultures and these subcultures change over time (Dilworth-Anderson and Gibson, 2002). Thus, the process becomes endless.

Nevertheless, many studies involving race and ethnicity have been performed, concerning the epidemiology, clinical course, risk factors and neuropathology of AD (reviewed in Shadlen et al., 2002). There have also been international studies comparing dark-skinned Caucasians in rural India with American Caucasians (e.g., Ganguli et al., 2000), and African Blacks with African-American Blacks (Hendrie, 2006). Rather than attempt a critical review of all of the work that has been done, findings from a number of these studies will be reviewed in an effort to address the following questions. Is the rationale adequate? What have we learned? Are we asking the right questions?

Rationale

There are scientific, public health, and ethical rationales for examining AD in the context of race and ethnicity. It is clear that manifestations and course of AD differ between individuals. In some individuals with AD, executive deficits are prominent; in others, including Alzheimer's Auguste D. (Alzheimer, 1907), psychotic symptoms predominate. It might reasonably be expected that there would be differences in prevalence, incidence, onset and course of AD in different racial groups based on different genetic heritage or between ethnic groups based on different life styles. This expectation is supported by Risch et al. (2002), who argue that that racial differences involve more than facial features, skin color, or nation or continent of origin; that they reflect a cluster of genetic factors that differentiate groups and make them a useful starting point for ascertaining the genetics of disease susceptibility and for

developing intervention strategies. Both Burchard et al. and Risch et al. argue further that through studying the effect of intermingling racial groups, much can be learned about the genetic predilection to diseases. For example, although we do not yet know what genetic factors account for the high prevalence of type II diabetes in Pima Indians, we do know it is somehow related to race, because intermarriage with Whites produces offspring less susceptible to type II diabetes (Williams et al., 2000).

Scientific rationale

The scientific rationale for examining AD in various races and ethnic groups is that causes or mitigating factors for the disease may differ from group to group and might lead to different preventive measures or treatments for different groups. Despite the 99.9% genetic similarity between persons of different racial groups, 0.1% of the 6 billion base pairs per cell amounts to 6 million base pairs per cell (Crow, 2002) and major differences do occur in the prevalence of many diseases. Some appear related to adaptive genetic mutations, such as the formation of S-hemoglobin, causing sickle cell disease in Blacks of African origin. The conformational effect of S-hemoglobin on red blood cell configuration may have had an adaptive function in Africa; protecting against the malaria parasite. The lethal mutation responsible for Tay-Sachs disease occurs frequently in descendants of eastern European Ashkenazi Jews, but appears to have had no adaptive function.

What about AD? In the case of AD, there is not yet evidence that the mutations in either of the presenilin genes causing autosomal dominant AD differ in frequency between racial or ethnic groups. The high prevalence of autosomal dominant AD in so-called Volga Germans appears related to the transmission of a mutated presenilin gene from a single founder (Bird et al., 1988), but there is preliminary evidence of varying rates of AD between racial groups and also of different impact of disease modifying factors, such as the apolipoprotein E ϵ 4 allele (Maestre et al., 1995).

Public health rationale

It is in public health that ethnicity/culture have major importance. Cultural beliefs and values must be considered in attempts to establish the concept of disease, to recognize specific diseases, seek treatment, and ultimately, to initiate preventive measures. In many cultures, including the American public until perhaps 20 years ago, progressive cognitive impairment was seen as a normal consequence of aging. Due to the educational efforts of the Alzheimer's Association, this perception has changed. Recruitment of subjects for study of AD can also lead to increased community awareness. Efforts by the UT Southwestern team to recruit Choctaw Indians led to an educational piece on AD and several news stories describing our studies in the monthly tribal newspaper. Our representatives have attended numerous health fairs, providing educational materials and performing memory checks; the latter serving as a source of referrals to our American Indian satellite clinics. Cholinesterase inhibitors for the treatment of AD were not in the Choctaw Nation formulary before the establishment of our clinic. And, as better treatments become available for AD, a treatable population will have been identified.

Finally, if aspects of life style such as diet and exercise can be shown to reduce the incidence or the impact of AD, the disease could be attacked by educational measures aimed at the populations at greatest risk. Such an educational campaign concerning obesity has been underway for a number of years in many American Indian communities as a means to prevent hypertension and type II diabetes (Davis et al., 1999).

Ethical rationale

The Belmont Report (1978) sets forth 3 principles as the ethical basis for human research; respect for persons, justice, and beneficence. Respect for persons indicates a need to understand and to take into account the belief systems of persons whom we wish to involve in research. Many of these are determined by ethnicity. Based on the ethical principle of justice, all racial and ethnic groups should have equal access to research and treatment. But there are limitations in the practical application of the principle of justice. The cost to society of studying certain groups may not be commensurate with the potential gain if these groups are geographically or culturally isolated. Should not the bulk of a society's resources be allocated in ways that will benefit the majority? To what length should society as a whole go to fairly include all racial and ethnic groups? A formulaic approach is employed by NIH; federally funded researchers are asked to include substantial minorities such as Hispanics and African Americans, at least to the extent that they are represented in the general population, or to justify their non-inclusion. The problem of whom to include is best illustrated by the ethnic category of Hispanic. These persons are racially and culturally heterogeneous. Racially, they tend to be mixtures of Native American, White, and African stock (Burchard et al. 2005). By what criteria should Hispanics be included as an ethnic group? Country of self or parental origin? Primary language of Spanish? And within the Hispanic community there are many subcultures; Puerto Rican, New York Puerto Rican, Cuban, Cuban American, Mexican, Mexican American, etc. Are these meaningful differences?

A perhaps more important consideration is that within all racial/ethnic groups are persons who live in poverty and as a consequence have poor education, poor access to information and medical care, and little likelihood of being included in medical research. Given the extensive evidence for a relationship between low education and AD (e.g., Stern et al., 1994), and following the ethical principal of beneficence, perhaps significant efforts should be expended to include in AD research these under represented and possibly more vulnerable persons.

Results

There are too many studies to adequately summarize in this perspective, so a few representative studies have been selected, beginning with comparisons of incidence, prevalence, and course of AD in different racial and ethnic groups. In one study, African Americans appeared to be at greater risk for AD than Caucasians (Whites) (Tang et al., 2001). In the age range from 65–74 years, the incidence rate per person-year was 1.7% for African Americans and 0.4% for Whites; from 75–84, 4.4% vs. 2.6%. By contrast, ethnicity may be a strong mediating factor within the Black race. In a population-based comparison of Nigerian Blacks and urban African Americans the age-adjusted prevalence of AD was 1.41% in Nigerian Blacks vs. 6.24% in urban African Americans (Hendrie et al., 1995).

There was no difference in the incidence and prevalence of AD in the Cardiovascular Health Study cohort (2,865 Whites and 492 African Americans) studied an average of 5.4 years (Fitzpatrick et al., 2004). Studies are contradictory with regard to the clinical course of AD in African Americans. A one-year follow up study comparing 82 African American with 935 White subjects showed essentially no difference in rate of progression on a neuropsychological test battery, but the dropout rate for African Americans over the one year was much higher than for Whites (44% vs. 18%) and may have introduced an element of bias (Fillenbaum et al., 1998). Some studies show more rapid progression in African Americans than in Whites (reviewed in Shadlen et al., 2002). However, a recent longitudinal study found that African Americans had a lower level of global cognition at baseline than did non-African Americans, but a 25% slower rate of cognitive decline (Barnes et al., 2005).

Chandra et al. (2001) found the overall incidence of AD in persons ≥ 65 years of age in rural India to be 4.7/1 000 person-years as compared with 17.5/1 000 in a largely White reference population in the Monongahela Valley of Pennsylvania, despite the fact that about 75% of the Indian subjects were illiterate, and that low educational achievement has been strongly associated with AD in many studies (e.g., Zhang et al., 1990; Gatz et al., 2005). Chandra et al. noted that all older adults in their Indian cohort lived with their families in a cognitively undemanding environment. Thus, many might not have met functional impairment criteria for dementia because of low family expectations or the traditional respect of Indians for their elders.

In a population-based study of reservation-dwelling Canadian Cree Indians, Hendrie et al. (1993) found AD to be less frequent in the Cree than in English-speaking Canadians; only one case of AD was identified among 192 Cree elders as compared with 20/252 elderly English-speaking Canadians. The age-adjusted prevalence rate was 0.5% in Cree Indians as compared with 3.5% in English speakers. In comparing 26 age-matched Cherokee Indians with and without AD, a significantly larger portion of the AD than the control group had American Indian heritage $\leq 50\%$, suggesting a possible protective effect of American Indian heritage against AD; the percentages were unchanged by the E ϵ 4 allele (Rosenberg et al., 1996). Weiner et al. (2003) found no difference in time from diagnosis to death between American Indians and Whites, but the modal American Indian in the study had only 25% American Indian heritage.

There are also racial differences in the inheritance and effects of the apolipoprotein E ϵ 4 allele, the most important risk factor (aside from age) for late-onset AD. Farrer et al. (1997) found that Japanese had a stronger association than Whites; African American and Hispanics had a weaker association than Whites, but there was significant heterogeneity in African Americans' odds ratios (Farrer et al., 1997). More recently, Graff-Radford et al. (2002) found an association of E ϵ 4 allele to AD similar in African Americans and Whites, while residents of rural India were found to have an E ϵ 4 allele association with AD similar to Whites (Ganguli et al., 2000). There was only a 4.5% E ϵ 4 allele frequency in an inbred Arab community in Israel with 20.5% AD prevalence in persons aged 65 or older (Farrer et al., 2003). A similar low prevalence of E ϵ 4 (7.3%) was noted in rural Indians with a very low incidence of AD (Chandra et al., 2001). Although inheritance of E ϵ 4 appears to induce earlier expression of AD in most groups (Daw et al, 2000) including African Americans (Graff-Radford et al., 2002), the relationship between E ϵ 4 in African Americans may only appear in the homozygous state (Chui and Gatz, 2005). Furthermore, Gureje et al. (2006) found no association between inheritance of E ϵ 4 allele and AD in Nigerian Blacks, suggesting that different risk or disease-modifying genetic factors might be operative in Nigerians. The picture is even further complicated by the finding that American Indians living in rural Mexico and characterized as physically active, consuming a low fat, high carbohydrate diet, did not have the increase in total or LDL cholesterol usually associated with E ϵ 4 in North American Indians (Aguilar et al., 1999).

Despite published literature suggesting better than 90% accuracy of the clinical diagnosis of AD in some series (Morris and Rubin, 1991), these criteria do not detect mixed pathology equally well. A recent unpublished autopsy review of 172 persons who had a clinical diagnosis of probable AD (McKhann et al. 1984) at the UT Southwestern Alzheimer's Disease Center showed that 90% had AD pathology, but 21.4% also had large numbers of cortical Lewy bodies. No difference has been found at autopsy between African Americans and Whites in the presence or number of infarcts, plaques, tangles, Lewy bodies or amyloid angiopathy (Wilkins et al., 2006).

We have learned, then, that there appear to be differences in the prevalence and incidence of AD in various racial and ethnic groups, and that these differences are often unrelated to presence of the Eε4 allele and that functional criteria for AD may not be met by persons living in a cognitively undemanding environment.

What are the right questions?

With regard to race, an important unasked question is whether there is sufficient racial homogeneity in the group under study. On a genetic basis, it does not seem appropriate to lump Asians with Pacific Islanders, as is done in the U.S. Census. We do not know the degree of African ancestry in most African Americans, but only 0.4% of African Americans indicated mixed racial heritage in the 2000 U.S. census (www.census.gov/population/www/cen2000). Hispanics are neither a racial nor a single ethnic group. A case can be made, however, for studying American Indians.

The case for studying American Indians

American Indians may have much to offer with regard to the influence of racial and cultural contributions to the pathogenesis of diseases such as AD. The primary advantage of American Indians from the racial standpoint is a document known as the Certified Degree of Indian Blood (CDIB). The CDIB, based on records from the tribal rolls, indicates the percentage (e.g., full blood, 50%, 25%, etc.) of an individual's American Indian heritage. The availability of such information can make it easier to quantify the effects of racial heritage on susceptibility to certain diseases. Within our group of American Indian AD subjects, we have shown that persons with American Indian heritage $\geq 50\%$ vs. those with American Indian heritage $< 50\%$ had significantly more frequent history of hypertension (76% vs. 46%, $\chi^2 = 7.138$, $p = .008$) and diabetes (50% vs. 10%, $\chi^2 = 15.142$, $p < .001$) (Weiner et al., 2003). It is probably no longer possible to study the interaction of race and cultural factors in Choctaws because their religion and diet is largely that of rural Whites, but it would be possible if more remote and less acculturated tribes of known blood quantum could be studied.

Conclusions

According to Collins (2004), self-identified race is the first link in a series of weak links leading to ancestral geographic origin, to genomic variation, to variation in disease-relevant alleles, and finally to individual disease risk. The studies cited here all fit with such a weak connection, but nevertheless suggest that the study of different racial groups has potential for illuminating the pathogenesis of AD. However, such studies clearly need exhaustive data gathering encompassing not only biological measures, but environmental (such as climate or exposure to toxins) and ethnicity-related life style measures (such as education, nutrition, and exercise) as well. A significant drawback of current racial and ethnic studies is lack of pathological confirmation of AD.

There appears to be scientific value in studying genetically homogeneous populations in which AD is highly prevalent (as in the Israeli Arabs) and to then determine if there is something in their common genetic makeup or in their environment (or the interaction between the two) that accounts for the excess prevalence of AD. It seems also worthwhile to search for groups with low incidence and prevalence of AD, and to then attempt to ascertain the factors that might account for this. On the other hand, experience with one Oklahoma Indian tribe was that having reported that they might have protection against AD (Rosenberg et al., 1996), they saw no need for further participation in research; AD was someone else's problem. Another approach is to search out families with high occurrence of late-onset AD, as in the NIA-funded Alzheimer's Disease Genetics Initiative

(

www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/NeuroscienceOfAging/ProgramInitiatives/ADGI.htm) that aims to collect genetic information from 1 000 affected families. The last method is the easiest and least expensive, because the families of these persons are highly motivated and do not require education to the concept of disease and the process of research. If racial elements then seem to play a role, further investigation could be made in a representative population from a specific racial group, rather than attempting to examine all racial groups and their cultural variants. If genetically homogeneous groups could be found, it would be possible to examine in a Framingham Study model (www.nhlbi.nih.gov/about/framingham/design.htm) the impact of racial mixing from generation to generation, a design suggested by Rowe (2005) to help distinguish between genetic and environmental factors (assuming similar life style), but a design that would exceed the lifespan of most investigators.

Based on information currently available, it seems unlikely that race-based studies will yield much useful information unless findings are stratified by degree of family heritage (in the case of diseases with founder effects) or racial heritage, especially in the U.S. where self-designated race may be misleading. For example, among persons self-designated in the 2000 census as American Indian or Alaska Native, 40% indicated a secondary race (www.census.gov/population/www/cen2000). As noted above, only 0.4% of African Americans indicate that they are of mixed racial heritage, but we have no objective way to know if the differences between urban U.S. African Americans and Nigerian Blacks are attributable to partial White ancestry rather than environmental factors. We would need to compare members of the same Nigerian families in the two different locations to answer this question. Until there is a biological marker for AD, studies of incidence and prevalence are also likely to be distorted by other factors, such as insensitivity of instruments or low social expectations of elders in certain cultures. (Chandra et al., 2001), and postmortem confirmation of AD diagnosis, at least in a subset of subjects, is imperative.

Study of the American Indian offers the possibility of a establishing a more meaningful relationship of race to disease or disease vulnerability markers by stratifying outcome variables according to degree of American Indian heritage.

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