EDITORIAL

Environmental Exposures and the Risk for Alzheimer Disease
Can We Identify the Smoking Guns?

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Over the past 3 decades, the focus on the molecular pathogenesis of Alzheimer disease (AD) has led to remarkable advances in our understanding of the emergence of symptoms and the course of the disease.[1] Biomarkers derived from growing knowledge of the pathobiology have enabled identification of amyloid plaques in both symptomatic and cognitively normal individuals,[2] the latter potentially identifying a population at high risk for dementia. About 20 genes have been identified as being associated with increased or decreased risk for late-onset AD (LOAD).[3] Most of these linked genes have been identified by genomewide association studies and meta-analyses.[3] Each new gene linked to LOAD fills in another gap in our understanding of AD pathogenesis and also serves as a new potential therapeutic opportunity.

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Each of the 20 LOAD genes exerts only a small effect on risk. The exception is the apolipoprotein E (*APOE*) ε4 allele, identified by linkage studies to a site on chromosome 19 and characterized with studies showing binding of the amyloid-β (Aβ) peptide to cerebrospinal fluid proteins. Apolipoprotein E is by far the most prevalent and potent LOAD genetic risk factor yet discovered: each copy of *APOE* ε4 triples the risk for AD. Additional alleles conferring LOAD risk with anything approaching the power of the ε4 allele are not anticipated based on the prediction that any susceptibility of equal or greater power as compared with *APOE* ε4 surely would have been identified by now.

Despite the advances in genetics and diagnostic markers, the variability in risk and the limited power of allelic risk candidates (beyond *APOE* ε4) have led increasingly to the conclusion that environmental factors and toxic exposures must also contribute significantly to the risk for developing LOAD. Some of these factors may well exert their actions via newly recognized pathways of DNA methylation and epigenetic modes of influence. The single most compelling piece of relevant data has emerged from the demonstration that monozygotic twins are usually discordant for AD and/or age at symptom onset,[4] providing prima facie evidence for nongenetic modulators. Identification of the important environmental influences that modulate AD risk represents the next great frontier for discovery. Are there smoking guns to be found on this frontier? Is environmental smoke one of them?

At the present time, among the classic (ie, exogenous) environmental factors, only head trauma has sufficiently robust data to qualify as a widely recognized and currently accepted risk (see our article[1] for review). Polygenic and/or acquired risk factors associated with increased or diminished risk for AD include vascular and metabolic factors (ie, body mass, blood cholesterol, and blood pressure), glucose homeostasis (ie, blood glucose and insulin resistance), and exercise (also reviewed in our article[1]). Many of these risks are relevant less at the age at onset of LOAD and more relevant if they have been present in midlife.

The situation in AD contrasts with that in Parkinson disease, another neurodegenerative disorder. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine and certain pesticides are now linked convincingly to the risk for Parkinson disease.[5] Among the best known historical associations of environmental toxins with dementing disorders were cycads in Guamanian amyotrophic lateral sclerosis (amyotrophic lateral sclerosis–Parkinson disease complex) and aluminum in AD. However, each of these putative toxin-causing dementia hypotheses has been challenged and, at present, neither is generally accepted to be an authentic association.

The presence of early olfactory and entorhinal pathology in AD has led to speculation that an inhaled agent might be implicated in initiating the disease given (1) the exposure of the olfactory neurons to the environment and their direct connections to the rhinencephalon and (2) the systemic access granted by alveolar entry. Recently, aerosolized vehicular combustion fumes[6] and secondhand smoke[7] have been implicated in both clinical epidemiological and neuropathological studies. Dramatic reports from Calderón-Garcidueñas et al[8] revealed diffuse amyloid plaques and inflammation in the brains of children and young adults residing in Mexico City, where the air quality ranks among the worst on the planet. Transcription of the Alzheimer amyloid precursor protein gene is regulated by acute phase reactant molecules, leading to rapid increases in the levels of amyloid precursor protein and its metabolite Aβ immediately following chemical or traumatic injury. Based on this well-documented phenomenon, one of us (S.G.) examined brain Aβ40 and Aβ42 levels in the brains of mice exposed to an inhaled toxin model of air pollution that used exposure to atmosphere containing aerosolized nickel nanoparticles (NiNPs).[9] Although we expected to see an elevation in brain Aβ following NiNP exposure, we were startled at the rapidity of the effect (ie, following 3 hours of exposure of the mice to NiNP). This immediate effect was consistent with

data reported by one of us (S.T.DeK.) showing rapid elevation and deposition of brain Aβ following severe traumatic brain injury.

Promotion of cerebral amyloidosis is not the only manifestation of inhaled toxin exposure. Davis and colleagues[6] demonstrated important damage to the hippocampal neurons of mice exposed to ambient levels of vehicular aerosols. These and other new frontier studies suggest that many new environmental, genetic, epigenetic, and interaction factors should be explored as a matter of public health stewardship.

In this issue of *JAMA Neurology*, Richardson and colleagues[10] demonstrated significant elevations of levels of dichlorodiphenyldichloroethylene (DDE), the major metabolite of dichlorodiphenyltrichloroethane (DDT), the common insecticide, in the brains of patients with AD. They also confirmed a strong correlation of serum levels of DDE with brain levels. While the use of DDT has been significantly restricted in the United States for decades (since the environmental damage revealed by Rachel Carson in *The Silent Spring*), the mean differences in DDE concentrations between AD cases and nondemented control brains were obvious, and some of the DDE levels observed in the AD brains were quite extraordinary.

There are weaknesses in the Richardson et al study,[10] and they are reflective of the typical difficulties in determining environmental risks and/or exposures, especially when exposures occur early in life but clinical manifestations do not appear until many decades later. Issues include (1) variability of the time of and duration of exposures; (2) individuals' recall of exposures; (3) timing of biological sampling; (4) stability of samples and compounds; (5) proximity of exposure to symptoms (especially of a disorder like AD, where pathological change may develop over decades and subsequent emergence of clinical symptoms is slow and insidious); and (6) how long after exposure the toxic agent (eg, lead in the bones or metabolites in the serum) can be identified. Importantly, variability in the effects of such exposures may also be affected by individual variation in the brain's reaction to the agent (eg, elevation of amyloid precursor protein and possibly Aβ by DDE, as proposed in this case) and by individual variation in absorption, distribution, metabolism, and excretion of the toxin, as suggested by Richardson et al.[10]

While the mean difference in DDE between AD cases and control participants was statistically significant when all cases were pooled, the Texas cohort drove the significance level. There was no difference in DDE levels in the cases and control participants from the Emory University cohort. While the authors proposed that the lack of significant difference in the Emory group was likely owing to the small number of cases, one might reasonably and logically ask why the strong relationship of levels of DDE to AD diagnosis in the Texas cohort was not equally likely to be spurious because of its small sample size. Nevertheless, the pooled data set reported here still yielded a statistically significant elevation of DDE in the AD brains (albeit at a lower but still robust level of significance). The authors cited other regions in the world where levels of DDE are extremely high (southern Spain and parts of India), but there are no data to suggest a cluster of higher AD prevalence in those regions. To be conservative, in our opinion, the Richardson et al report should be noted but, for now, these conclusions should be considered as preliminary until there is independent confirmation in other populations.

A fuller understanding of the environmental risks of AD will require sample collection and clinical observations over long periods. However, it is imperative that researchers and research administrators collaborate to determine what samples already stored from large epidemiological or therapeutic studies should be evaluated and what potential exposures should be sought. Studies in which samples have already been collected (eg, those available at the National Central Repository for Alzheimer Disease, the Framingham Heart Study, and others) might provide heuristic insights. Because the DDT/DDE data already suggest that brain levels correlate closely with serum levels,[10] samples from a number of studies in which cognition and dementia are tracked over years (eg, the Alzheimer Disease Neuroimaging Initiative Biomarker Core) could be deployed quickly for studies aimed at confirming or refuting the Richardson et al report.[10] In this context, Richardson and colleagues have provided both a wake-up call to explore environmental influences and pointed us to a first area to assess—pesticides, which have already been implicated in other human illnesses.

New longitudinal epidemiological studies planning human participant biological sample acquisition should also consult with dementia researchers and National Institutes of Health administrators from the National Institute on Aging, the National Institute of Neurological Diseases and Stroke, and the National Institute on Environmental Health Sciences to assess what samples and clinical observations might be collected for such cognitive risk markers. This would ensure that such valuable samples are obtained and stored properly to avoid contamination and/or degradation. These considerations proved critical in the early days of trying to sample trace metals in serum and brain. Given the increasing evidence that AD, like atherosclerosis, is most importantly a disease of middle age, planning for new studies and examination of samples from prior longitudinal studies of midlife offer new opportunities to study exposures, genetics, and epigenetics, as well as to develop new weapons for treating and/or preventing AD. Important evidence about new environmental toxin-related cascades or final common pathways leading to neurodegeneration can serve as strategies for AD prevention and inform research on other neurodegenerative diseases.

In the past, many consensus panels on future directions in AD research have recommended further studies of environmental contributors to the development of dementia. Now that straightforward genetic approaches appear to be less likely to yield new and powerful effects on AD, the time has arrived to direct resources toward the formation of collaborative teams of epidemiologists, toxicologists, geneticists, and dementia researchers. To realize this goal, the National Institute on Environmental Health Sciences has recently issued R01 and R21 program announcements in this area. Collaborations across

National Institutes of Health institutes, as well as public-private partnerships, may result in the fastest and most fruitful efforts to track down the toxic smoke to which millions of people might be exposed and achieve smoking gun control—ie, diminution of important environmental risks and reduction of the risk for the development of AD.

ARTICLE INFORMATION

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