Studies examine prevalence of amyloid among adults and its link with cognitive impairment

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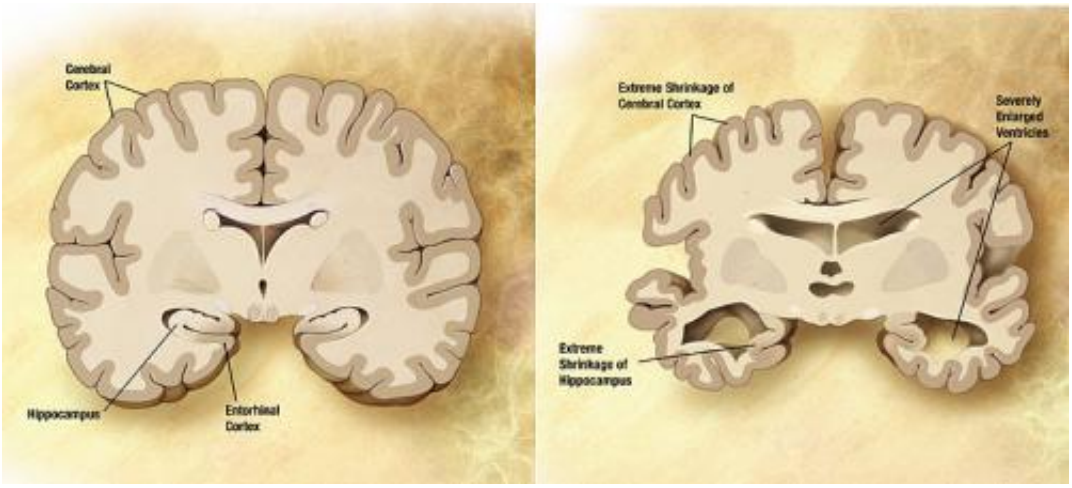

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Two studies in the May 19 issue of *JAMA* analyze the prevalence of the plaque amyloid among adults of varying ages, with and without dementia, and its association with cognitive impairment.

Alzheimer disease (AD) is the most common cause of dementia, with a worldwide prevalence of about 25 million in 2010, expected to be doubled by 2030 because of increased life expectancy. The earliest recognizable pathological event in AD is cerebral amyloid-β aggregation

(protein fragments that clump together to form plaque). This pathology may be present up to 20 years before the onset of dementia. Prevalence estimates of amyloid pathology in persons without dementia are needed to better understand the development of AD and to facilitate the design of AD prevention studies. Initiation of treatment for AD in the pre-dementia phase, when neuronal damage is still limited, may be crucial to have clinical benefit.

In one study, Willemijn J. Jansen, M.Sc., and Pieter Jelle Visser, M.D., Ph.D., of Maastricht University, Maastricht, the Netherlands and colleagues used individual participant data meta-analysis to estimate the prevalence of amyloid pathology as measured with biomarkers (on positron emission tomography or in cerebrospinal fluid) in participants with normal cognition, subjective cognitive impairment (SCI), or mild cognitive impairment (MCI). Databases were searched to identify relevant biomarker studies, which were included if they provided individual participant data for participants without dementia. Individual records were provided for 2,914 participants with normal cognition, 697 with SCI, and 3,972 with MCI (ages 18 to 100 years) from 55 studies.

The researchers found that the prevalence of amyloid pathology increased from age 50 to 90 years from 10 percent to 44 percent among participants with normal cognition; from 12 percent to 43 percent among patients with SCI; and from 27 percent to 71 percent among patients with MCI. Apolipoprotein E (APOE)-ε4 (a gene associated with an increased risk of developing AD) carriers had 2 to 3 times higher prevalence estimates than noncarriers. The age at onset of amyloid positivity was associated with cognitive status and the APOE genotype. At age 90 years, about 40 percent of the APOE-ε4 noncarriers and more than 80 percent of APOE-ε4 carriers with normal cognition were amyloid positive.

The researchers write that this study has several implications for

understanding the development of AD. "The observation that key risk factors for AD-type dementia are also risk factors for amyloid positivity in cognitively normal persons provides further evidence for the hypothesis that amyloid positivity in these individuals reflects early AD. ... Our study also indicates that development of AD pathology can start as early as age 30 years, depending on the APOE genotype. Comparison with prevalence and lifetime risk estimates of AD-type dementia suggests a 20- to 30-year interval between amyloid positivity and dementia, implying that there is a large window of opportunity to start preventive treatments."

The authors note that the exact interval between the onset of amyloid positivity and onset of AD-type dementia needs to be assessed by long-term follow-up studies because not all persons with amyloid pathology will become demented during their lifetime, and not all individuals with a clinical diagnosis of AD-type dementia have amyloid pathology. "Because of the uncertainty about whether and when an amyloid-positive individual without dementia will develop dementia, amyloid positivity in these individuals should not be equated with impending clinical dementia but rather be seen as a risk state. Our prevalence rates can be used as an inexpensive and noninvasive approach to select persons at risk for amyloid positivity."

In another study, Rik Ossenkoppele, Ph.D., of VU University Medical Center Amsterdam, the Netherlands, and colleagues used individual participant data meta-analysis to estimate the prevalence of amyloid positivity on positron emission tomography (PET) in a wide variety of dementia syndromes.

The clinical utility of amyloid PET imaging is potentially limited by a proportion of patients with non-AD dementia and cerebral amyloid-β plaques. To correctly interpret the clinical significance of amyloid PET results, clinicians need to understand the prevalence of amyloid

positivity across different types of dementia and how this is associated with demographic, genetic, and cognitive factors. Most amyloid PET studies to date come from single centers with modest sample sizes, according to background information in the article.

After a search of databases for amyloid PET studies, the authors included data for 1,359 participants with clinically diagnosed AD and 538 participants with non-AD dementia. The reference groups were 1,849 healthy control participants (based on amyloid PET) and an independent sample of 1,369 AD participants (based on autopsy).

In AD dementia, the average prevalence of amyloid positivity was 88 percent. The prevalence decreased with age from 93 percent at age 50 to 79 percent at age 90. This association differed according to APOE ε4 status. In APOE ε4 carriers, the prevalence remained at least 90 percent regardless of age, whereas the prevalence in noncarriers declined from 86 percent at age 50 years to 68 percent at age 90 years. Similar associations of age and APOE ε4 with amyloid positivity were observed in participants with AD dementia at autopsy. In most non-AD dementias, amyloid positivity increased with both age (from 60 to 80 years) and APOE ε4 carriership.

"The main findings of this individual participant meta-analysis were that the prevalence of amyloid on PET decreased with age in participants diagnosed with AD (greatest in APOE ε4 noncarriers) and increased with age in most non-AD dementias. The convergence of amyloid positivity across dementias with increasing age suggests that amyloid imaging might have the potential to be most helpful for differential diagnosis in early-onset dementia, particularly if the goal is to rule-in AD dementia," the authors write.

"However, the high concordance between PET and pathology suggests that amyloid imaging might have the potential to be used to rule-out AD

dementia regardless of age. Furthermore, amyloid in non-AD dementia may be clinically important as amyloid positivity was associated with worse global cognition. Data from this study may inform research into the clinical application of amyloid PET and highlight the necessity of biomarker-based participant selection for clinical trials."

"Jansen et al and Ossenkoppele et al provide succinct meta-analyses of considerable clinical value," writes Roger N. Rosenberg, M.D., of the University of Texas Southwestern Medical Center at Dallas, and Editor, *JAMA Neurology*, in an accompanying editorial.

"Persons without dementia have an increasing prevalence of cerebral amyloid pathology with age, APOE genotype, and cognitive loss as measured by PET imaging or cerebrospinal fluid findings. Similarly, among persons with dementia, the prevalence of amyloid pathology was related to clinical diagnosis, age, and APOE genotype. Together, these data show the immense potential clinical use of amyloid imaging to make the correct diagnosis in early-onset dementia and, more specifically, to establish the diagnosis of AD-type dementia and noncarrier APOE-ε4 genotype among persons older than 70 years."

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