A race effect on amyloid deposition?

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The development of PET radiotracers, allowing visualization of amyloid in the brains of living patients, has been a major breakthrough in the field of Alzheimer disease (AD). For example, the presence of amyloid in the brain at a preclinical/predementia stage may not be sufficient for developing AD, but is associated with increased risk for progression to AD dementia.[1] The identification of determinants of amyloidogenesis and factors that influence the prevalence and risk of brain amyloid positivity is crucial for several reasons: (1) to help understand the physiopathology of the disease and more specifically the cause of β-amyloid accumulation (which would in turn help develop disease-modifying treatments); (2) to define target populations for clinical trials testing antiamyloid drugs and develop trial endpoints; and (3) to act on these β-amyloid determinants (e.g., on modifiable lifestyle factors) to decrease the prevalence and risk of brain amyloid positivity. The main known determinants of amyloid positivity in populations without dementia are age (with prevalence from 50 to 70 years increasing from 10% to 44% in cognitively normal individuals and from 27% to 71% in patients with mild cognitive impairment [MCI]) and *APOE* ε4 (with 2–3 times higher prevalence in carriers than noncarriers).[2] Education/cognitive activity is often thought to modulate amyloid burden in interaction with age, while the influence of sex on amyloid deposition is less clear.[3]

In this issue of *Neurology*®, Gottesman et al.[4] assessed whether brain amyloid deposition measured with florbetapir PET is associated with age, sex, race, education, and *APOE* ε4 in a community-based cohort without dementia. The study included 329 elderly participants (including 141 black participants), ranging from cognitively normal to MCI, and recruited from 3 US sites. They found higher florbetapir uptake associated with age, female sex, and *APOE* ε4 carrier status, all consistent to various extents with previous reports. In addition—and this is the novel finding in this article—the authors reported an effect of race, such that black individuals were more likely to be amyloid-positive and have higher cortical florbetapir uptake compared to white participants. This analysis by race was stimulated by the fact that previous studies reported increased prevalence of AD, more mixed pathologies at autopsy (more vascular disease), and lower influence of *APOE* ε4 in black compared to white individuals.[5,6] In the study by Gottesman et al., vascular factors and *APOE* ε4 did not seem to be related to increased florbetapir uptake in black participants. If confirmed, these results would have important implications, as the effect of race might reflect genetic predisposition or higher exposure to risk factors. Future studies investigating the underlying mechanisms for this race effect might thus ultimately help clarify the mechanisms and risk factors for amyloidogenesis and AD.

Yet caution is needed in the interpretation of these findings, pending replication in independent and well-controlled studies. Indeed, alternative interpretations of the findings should be kept in mind given several substantial potential confounds. While the black participants recruited to this study may have had increased florbetapir uptake, they also had lower cognitive functioning (Mini-Mental State Examination [MMSE] score), more hypertension, lower education, and lower intracranial volume. All of these factors are associated with increased risk for AD or amyloid positivity.[2,3,7,8] The higher brain florbetapir uptake in black compared to white participants thus might simply reflect the differences in the recruited samples. Some of these factors were controlled individually, but even this does not fully control for the risk that the black participants might have been recruited with lower general health and lower socioeconomic status, and represent a different sample of the population than the white participants. Indeed, the effect of race was no longer significant when correcting for the MMSE score, which tends to suggest that race alone may not be responsible for increased amyloid in black participants. Finally, 96% of the black participants were recruited from a single site, while all white participants were from the 2 other sites. It is thus impossible to know whether the differences were due to the race or to specific characteristics of the site.

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This possible site effect might reflect a geographical difference (e.g., higher exposure), a difference in florbetapir measurement, or both. Indeed, black participants from this site had higher florbetapir values (n = 135, median standardized uptake value ratio [SUVR] 1.25) than black participants from the other sites, although very small in number (n = 6, median SUVR 1.20), and values in the latter were closer to the florbetapir values of the white participants (median SUVR 1.17).

This study is provocative as it suggests for the first time that there might be race differences in the process of amyloid deposition. This observation will hopefully motivate future works on this topic, and if replicated, lead to further investigations of the reasons for this effect and help clarify the neurobiologic basis for amyloidogenesis.

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