From Alois to Amyvid

Seeing Alzheimer disease

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When Alois Alzheimer first described the neuropathologic hallmarks of his eponymous disease (Alzheimer disease [AD]) in 1906,[1] the possibility of detecting amyloid plaques in vivo was unimaginable. About a century later, this became a reality when Klunk and colleagues[2] demonstrated that the ^{11}C-labeled PET tracer Pittsburgh compound B (PiB) selectively bound to fibrillar β-amyloid (Aβ) and revealed amyloid pathology noninvasively in subjects with AD. However, due to its short half-life of 20 minutes and difficult manufacturing process, ^{11}C-PiB had no prospect for widespread use. ^{18}F-labeled Aβ ligands are easier to deploy broadly, and several candidates have been studied in clinical trials.[3] With the recent Food and Drug Administration approval of the first of them, florbetapir (Amyvid, or AV-45), we are now effectively entering the era of clinical amyloid imaging. Like PiB, florbetapir accurately predicts whether or not fibrillar Aβ pathology will be present at autopsy.[4]

In this issue of Neurology®, Doraiswamy et al.[5] present the first longitudinal data for florbetapir. This multicenter study features an initial cohort of 151 participants, across a diagnostic spectrum, who underwent both florbetapir scans and cognitive/functional testing at baseline. Of those, 140 returned for an 18-month follow-up assessment (67 cognitively normal [CN], 46 with mild cognitive impairment [MCI] defined in a way to approximate nonresearch settings, and 27 with AD dementia at baseline). Florbetapir scans were rated qualitatively (positive or negative) and quantitatively (comparing cerebral uptake to the cerebellum, a reference region unaffected in AD). Florbetapir-positive subjects with MCI had greater declines across most cognitive and functional measures than their florbetapir-negative peers; similar results emerged from the quantitative method of florbetapir scan analysis. Rates of decline among subjects with AD dementia and CN subjects depended much less upon florbetapir status, although it is notable that florbetapir-positive CN subjects did exhibit greater declines by 2 important metrics, the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog, a multidomain cognitive battery) and the Clinical Dementia Rating scale, Sum of Boxes (CDR-SB, a multidomain rating scale). There was a trend for florbetapir positivity to predict a greater risk for MCI-to-AD dementia conversion at follow-up, but this was not significant. Unlike most studies, in which MCI is narrowly defined by a psychometric threshold, this study included any patient with a cognitive complaint (memory or otherwise) corroborated by an informant, with no requirement for an objective deficit. Therefore, the risk of decline associated with florbetapir positivity will likely generalize to MCI patients encountered in everyday clinical practice.

This study suggests that florbetapir—and amyloid imaging generally—may be clinically useful at informing prognosis as well as diagnosis. The findings are largely compatible with recent longitudinal studies using PiB,[6] with one notable exception: there was a low rate of florbetapir positivity (68%) among subjects with clinically diagnosed AD dementia in the present study. While poor sensitivity of florbetapir to plaque pathology could explain this finding, the Phase III data suggest a high negative predictive value[7] and support an alternative explanation, that 10 of 31 study participants with diagnoses of AD dementia actually had another etiologic diagnosis. The fact that florbetapir status did not correlate with the rate of cognitive or functional decline among the patients with dementia in this study is not necessarily surprising; whether due to AD or another illness, each patient had some progressive neurocognitive condition. In addition to teaching us humility, the high rate of florbetapir-negative dementia cases highlights a potential use of amyloid imaging in the clinic: it may help to spare clinically misdiagnosed patients from the cost or side effects of anti-amyloid therapies that are now in late-stage clinical development. And a negative florbetapir scan may trigger a more in-depth search for the right diagnosis, possibly boosting detection of reversible causes of dementia.

One note of caution: interrater reliability for qualitative florbetapir scan analysis was suboptimal in this study. New training guidelines have been developed to overcome this problem, but it is not yet clear how reliable image analysis will be in the community. Automated, quantitative tools for scan analysis could help clinicians to avoid subjective pitfalls of qualitative reads.[8]

Doraiswamy et al. show that florbetapir may play a clinically useful role in predicting the risk of cognitive decline among patients with MCI, lending credibility to recently proposed criteria for MCI due to AD.[9] In patients who have already crossed the threshold to dementia, the lack of a close association between florbetapir and cognitive/functional status is not surprising since 1) Aβ burden appears to remain fairly constant once amyloid positivity is reached, and 2) amyloid burden is no longer the driving force for disease progression once the clinical diagnosis of AD has been reached.[10] Its use in such patients will therefore be restricted to differential diagnosis. For cognitively normal individuals, there is not yet a role for amyloid imaging in screening for AD risk. Longer longitudinal follow-up will further clarify the prognostic utility of amyloid imaging, but for now, this study marks a milestone in our understanding of the role of amyloid imaging in our clinics.

DISCLOSURE

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