Brain-penetrating ACE inhibitors and Alzheimer disease

Ohrui et al. found that brain-penetrating angiotensin-converting enzyme (ACE) inhibitors significantly slow the rate of cognitive decline in Alzheimer disease (AD) patients with hypertension compared with other antihypertensive drugs.

see page 1324

Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression: A handful of ACEs?

Commentary by David S. Knopman, MD

The Ohrui et al. clinical trial is based on the novel hypothesis that there is an alteration in ACE in AD. Drugs that inhibit ACE are readily available, including at least two, perindopril and captopril, that cross the blood-brain barrier. Ohrui et al. randomized 162 hypertensive mild to moderate AD patients to one of these two brain-penetrating ACE inhibitors (ACE-I), or a non-brain-penetrating ACE-I or calcium-channel blockers, and followed them for 1 year. The Mini-Mental State Examination was the sole outcome measure. Patients treated with the brain-penetrating ACE-Is did not decline while patients in the other two groups experienced large declines.

There are links between the treatment effect of brain-penetrating ACE-I and emerging evidence about microvascular mechanisms in AD¹ as well as an overrepresentation of certain polymorphisms in the ACE gene in AD.² The recently described reduction in dementia incidence with perindopril and indapamide in a large prospective study³ is also consistent with the findings here. This study's findings are provocative and exciting, but readers must be skeptical. There are a number of methodologic weaknesses in the study. It is not clear whether perindopril, capto-

pril, or both drove the effect. The amount of decline in the other two groups was much larger than expected. The lack of adverse events is surprising and the extremely high retention rate of patients in both arms of the study is unusual. Moreover, despite the randomization, the medications were not administered in a blinded fashion. At this point, the reviewers and editors concluded that this provocative work should be published. However, the findings with ACE-Is must be replicated in carefully controlled, randomized, blinded studies.

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See page 1324

Neurology[®]

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