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Expanding ventricles may detect preclinical Alzheimer disease

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Although there are no treatments that slow the progression of Alzheimer disease (AD), therapies aimed at brain amyloid or at other mechanisms are in trials. It will be important to start treatment early in the process to prevent cognitive decline, emphasizing the importance of identifying AD at the earliest stage possible. Early detection of AD may be possible because asymptomatic subjects have amyloid plaques, intraneuronal tangles, and neurodegeneration.[1] PET scanning with C-11 Pittsburgh compound B[2] found evidence for amyloid accumulation in the brain of about 20% of healthy elders, FDG PET and MRI changes have been described in asymptomatic cognitively normal subjects, which seem to "predict" future cognitive decline and conversion to AD,[3] and amyloid, tau, and other biomarkers in CSF of cognitively normal subjects also suggest early AD.[4] None of these biomarkers is closely or directly correlated with neuronal loss.

Subjects with AD have less brain tissue in the hippocampus[5] and other brain regions,[6] associated with ventricular enlargement.[7] Furthermore, AD and mild cognitive impairment (MCI), which is accepted as a precursor to AD, are both associated with rates of tissue atrophy[8] and ventricular enlargement that are much greater than seen in the normal elderly population. Thus, brain shrinkage measured by MRI seems to be a reasonable surrogate for neurodegeneration. Structural MRI, ^{18}FDG PET, C-11 PIB PET, CSF biomarkers, and clinical assessments are part of the NIA-AD Neuroimaging Initiative, being conducted in 57 sites in the United States and Canada.[9]

In this issue of *Neurology*®, the study by Carlson et al.[10] substantially adds to the body of evidence that early signs of neurodegeneration can be detected in asymptomatic subjects, and that these changes predict future cognitive decline. The Oregon Brain Aging Study[11] follows a cohort of normal healthy subjects with clinical, neuropsychological, and imaging examinations. They measured longitudinal changes and examined differences in the rates of change of those elders who remained cognitively normal and those who become impaired. Studies of 79 individuals, enrolled as cognitively normal elders, were seen every 6 months for up to 15 years. It is very important to note that in this study, MCI was defined as at least two consecutive scores on the Clinical Dementia Rating Scale of 0.5 or greater, which is different from published diagnostic criteria for MCI.[12] Using MRI, the rate of change of brain ventricular volume was assessed. The major results of this report are that "the brain loss trajectory of subjects developing MCI during follow-up differed from healthy aging in a two phase process." The rate of ventricular expansion decreased with age. However, in the 37 subjects who subsequently developed MCI, the rate of ventricular volume expansion was greater than in those who did not develop MCI, and "an acceleration of ventricular volume expansion occurred on average 2.3 years prior to the clinical diagnosis of MCI." The authors

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conclude, with some justification, that “MR imaging may be used in detecting changes in association with AD prior to clinical measures” and suggest that “there are specific windows for optimal timing of introduction of dementia prevention therapies in the future.”

Taken together with the prior literature, the current results provide strong evidence that increased rates of neurodegeneration caused by AD pathology may be detected with structural MRI, prior to the development of symptoms or cognitive impairment. However, several limitations should be kept in mind. The results are unreplicated and may not be completely generalizable to other populations. The endpoint of MCI was defined as two consecutive CDR scores of 0.5 to ensure that the subjects had persistent decline. It will be of interest to know when and how many actually convert to frank AD. We are not provided with change data of neuropsychological tests, or measures of specific brain volumes, but we can expect this information to come in future publications.

The authors have shown that the rate of ventricular expansion, a measure which correlates with neurodegeneration, increases in normal elders beginning up to a decade before any sign of cognitive change measured by neuropsychological tests or careful informant based interview is detected. About 2 years prior to clinical detection of MCI there is a more rapid acceleration of brain atrophy. The results support the conclusion that longitudinal measurements of brain ventricular volume can be detected very early, and that such measurements may be used to select subjects for enrollment in clinical trials aimed at prevention of AD. It is even possible that, once we have approved treatments which slow the progression of AD in demented and MCI subjects, clinicians may employ longitudinal measures of the brain to identify normal elders with the earliest manifestations of AD, for effective preventative therapy. We can only hope that AD prevention becomes a reality for the future health of our patients, our family, and for the readers of this journal.

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