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Notes: IMPORTANCE: The appearance of beta-amyloidosis and brain injury biomarkers in cognitively normal (CN) persons is thought to define risk for the future development of cognitive impairment due to Alzheimer disease (AD), but their interaction is poorly understood. OBJECTIVE: To test the hypothesis that the joint presence of beta-amyloidosis and brain injury biomarkers would lead to more rapid neurodegeneration. DESIGN Longitudinal cohort study. SETTING: Population-based Mayo Clinic Study of Aging. PARTICIPANTS: One hundred ninety-one CN persons (median age, 77 years; range, 71-93 years) in the Mayo Clinic Study of Aging who underwent magnetic resonance, fludeoxyglucose F 18 (FDG) positron emission tomography (PET), and Pittsburgh Compound B (PiB) PET imaging at least twice 15 months apart. Participants were grouped according to the recommendations of the National Institute on Aging-Alzheimer Association preclinical AD criteria based on the presence of beta-amyloidosis, defined as a PiB PET standardized uptake value ratio (SUVR) greater than 1.5, alone (stage 1) or with brain injury (stage 2 + 3), defined as hippocampal atrophy or FDG hypometabolism. We also studied a group of patients with mild cognitive impairment (n = 17) or dementia (n = 9) from the Mayo Clinic Study of Aging or the Mayo Alzheimer Center with similar follow-up times who had undergone comparable imaging and had a PiB PET SUVR greater than 1.5. MAIN OUTCOMES AND MEASURES: Rate of change of cortical volume on volumetric magnetic resonance images and rate of change of glucose metabolism on FDG PET scan results. RESULTS: There were 25 CN participants with both high PiB retention and low hippocampal volume or FDG hypometabolism at baseline (preclinical AD stages 2 + 3). On follow-up scans, the preclinical AD stage 2 + 3 participants had greater loss of medial temporal lobe volume and greater glucose hypometabolism in the medial temporal lobe compared with the other CN groups. The changes were similar to those in the cognitively impaired participants. Extratemporal regions did not show similar changes. CONCLUSIONS AND RELEVANCE: Higher rates of medial temporal neurodegeneration occur in CN individuals who, on their initial scans, had abnormal levels of both beta-amyloid and brain injury biomarkers. Although preclinical AD is currently only a research topic, the description of its brain structural changes will be critical for trials designed to prevent or forestall dementia due to AD
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Notes: Persons with mild cognitive impairment (MCI) have overt changes in thinking and memory, but they are still largely independent in daily affairs. They have a far higher rate of developing dementia (progressing to a more debilitating state of cognitive impairment) than cognitively normal persons, but at the individual patient level, prognosis is variable. Sometimes persons with MCI do not worsen and a few even revert back to cognitive normality.(1,2) The variable prognosis in MCI is one reason why the term "MCI" has caught on: not only does it denote a sense of severity at the mildest level, it also conveys uncertainty of prognosis. Identification of the subset of patients with MCI at highest risk to progress to more severe cognitive impairment is a very important goal for research and future clinical care. Quantitating the degree of cognitive impairment by traditional history-taking, brief mental status testing, and more detailed neuropsychological assessment are necessary and informative first steps. However, knowledge of cognitive and functional status in MCI still leaves much uncertainty regarding the ability to predict worsening

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Notes: OBJECTIVE: The new criteria for preclinical Alzheimer disease (AD) proposed 3 stages: abnormal levels of beta-amyloid (stage 1), stage 1 plus evidence of brain injury (stage 2), and stage 2 plus subtle cognitive changes (stage 3). However, a large group of subjects with normal beta-amyloid biomarkers have evidence of brain injury; we labeled them as the "suspected non-Alzheimer pathophysiology" (sNAP) group. The characteristics of the sNAP group are poorly understood. METHODS: Using the preclinical AD classification, 430 cognitively normal subjects from the Mayo Clinic Study of Aging who underwent brain magnetic resonance (MR), (18) fluorodeoxyglucose (FDG), and Pittsburgh compound B positron emission tomography (PET) were evaluated for FDG PET regional volumetrics, MR regional brain volumetrics, white matter hyperintensity volume, and number of infarcts. We examined cross-sectional associations across AD preclinical stages, those with all biomarkers normal, and the sNAP group. RESULTS: The sNAP group had a lower proportion (14%) with apolipoprotein E epsilon4 genotype than the preclinical AD stages 2 + 3. The sNAP group did not show any group differences compared to stages 2 + 3 of the preclinical AD group on measures of FDG PET regional hypometabolism, MR regional brain volume loss, cerebrovascular imaging lesions, vascular risk factors, imaging changes associated with alpha-synucleinopathy, or physical findings of parkinsonism. INTERPRETATION: Cognitively normal persons with brain injury biomarker abnormalities, with or without abnormal levels of beta-amyloid, were indistinguishable on a variety of imaging markers, clinical features, and risk factors. The initial appearance of brain injury biomarkers that occurs in cognitively normal persons with preclinical AD may not depend on beta-amyloidosis.
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Notes: BACKGROUND: Defining the nature of the contribution of stroke to cognitive impairment remains challenging. OBJECTIVE: To describe associations between stroke history, APOE genotype, and subtypes of mild cognitive impairment (MCI). METHODS: We randomly selected residents from Olmsted County, Minnesota, aged 70 to 89 years on October 1, 2004, and invited eligible subjects without documented dementia to participate. Participants (n = 2050) were evaluated through an informant interview, a neurological evaluation, and neuropsychological testing. Neuropsychological testing included 9 tests to assess memory, attention, executive function, visuospatial cognition, and language. Subjects were diagnosed by consensus as cognitively normal or as having MCI (either amnesic or nonamnesic) or dementia. A history of stroke was obtained from the subjects and confirmed in their medical records. We computed the odds ratios (ORs) for a clinical diagnosis of MCI or for scoring in the lowest quartile on each cognitive domain. RESULTS: There were 1640 cognitively normal subjects and 329 subjects with MCI: 241 with amnesic MCI and 88 with nonamnesic MCI. In fully adjusted models with only subjects without dementia, a history of stroke was associated with a higher OR of nonamnesic MCI (OR, 2.85; 95% confidence interval [CI], 1.61-5.04) than amnesic MCI (OR, 1.77; 95% CI, 1.14-2.74). A history of stroke was also associated with impaired function in each cognitive domain except memory. The association was strongest for attention and executive function (OR, 2.48; 95% CI, 1.73-3.53). APOE epsilon4 genotype was associated only with amnesic MCI and with impaired memory function. CONCLUSIONS: In this population-based sample of persons without dementia, a history of stroke was particularly associated with nonamnesic MCI and impairment in

nonmemory cognition. The APOE epsilon4 genotype was associated with memory impairment and amnesic MCI

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Notes: BACKGROUND: Measurement of volumetric changes with MR might be a useful surrogate endpoint for clinical trials in frontotemporal lobar degeneration (FTLD). Because there is only limited longitudinal imaging data currently available, we measured the rate of change over 1 year of whole brain volume (WBV) and ventricular volume (VV) in patients with FTLD. METHODS: Subjects with an FTLD cognitive syndrome were recruited from five centers using standard clinical diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia (PNFA), semantic dementia (SMD), and progressive logopenic aphasia. Structural brain imaging, using three-dimensional T1-weighted sequences at 1.5 teslas, and cognitive, behavioral, and functional assessments were performed at baseline and approximately 1 year later. The boundary shift integral algorithm was used to determine change in WBV and VV. RESULTS: There were 76 patients (mean age 64 years; 41 men and 35 women) who had usable baseline and annual scans. The group-wise annualized change was -1.62% (SD 1.03, range +0.69 to -3.6) for WBV and 11.6% (SD 5.9, range -1.3 to 23.9) for VV. Rates of change were similar among bvFTD, PNFA, and SMD groups. Longitudinal changes in WBV and VV were correlated with decline on clinical global and cognitive measures. CONCLUSIONS: Multicenter, serial measurements of whole brain volume (WBV) and ventricular volume (VV) from magnetic resonance scans were feasible in patients with frontotemporal lobar degeneration (FTLD). Using WBV or VV as outcome measures would require recruiting (at 80% power) 139 or 55 subjects per group to detect a small (25%) or medium-sized (40%) effect in a randomized, placebo-controlled trial of a putative agent for FTLD
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- 12 Knopman, D. S. (1998). Dementias lacking distinctive histology. In A.Kertesz & D. G. Munoz (Eds.), *Pick's disease and Pick complex* (pp. 169-181). New York: Wiley.
Notes: DLDH is a pathologically defined entity that may represent one etiological molecular mechanism but more likely represents several. Over the next decade, we can expect that more and more familial dementing disorders with DLDH pathology will be linked to specific genes. The relationship of DLDH to disorders with distinctive histopathological features, in particular PiD with Pick bodies and ballooned neurons, remains to be clarified. While it is obvious that they share a clinical phenotype and some aspects of the pathological phenotype (mainly the topographic distribution of cell loss), Pick body-positive PiD and DLDH have an uncertain relationship. (Original description: Knopman et al., 1990, *Neurology* 40:251-6)

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Notes: Department of Neurology, University of Minnesota, Minneapolis From a series of 460 dementia patients referred to a regional brain bank, 14 (3%) patients had a pathologic diagnosis of primary degeneration of the brain involving multiple sites (frontoparietal cortex, striatum, medial thalamus, substantia nigra, and hypoglossal nucleus), with cell loss and astrogliosis. There were no neuronal inclusions and essentially no senile plaques. This entity, which we have termed "dementia lacking distinctive histology" (DLDH), presented with memory loss and personality changes, and led to death, usually within 2 to 7 years. Dysarthria and dysphagia were prominent in the later phases of the illness in most patients. The psychometric findings of some of the patients were consistent with a "frontal" lobe dementia. A few patients had prominent caudate atrophy on CT as well as neuropathologically. Eight of our patients had positive family histories for neurologic disease, mainly dementia. DLDH, in addition to Pick's disease, is a major member of the frontal-lobe dementia group. In patients under age 70 years, the frontal lobe dementias represent an important diagnostic consideration
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Notes: The most common early deficit in patients with Alzheimer's disease (AD) is in recent memory. Distinguishing patients with AD from normal elderly individuals, using currently available memory tests, is limited by their lack of suitability for bedside use or for large-scale screening. We have devised a new memory test, a delayed word recall (DWR) test, that is both brief and efficient. It was designed specifically to maximize the likelihood of poor performance in patients with AD and minimize the likelihood of poor performance in normal elderly subjects. The DWR test uses required elaborative processing of to-be-remembered words and delayed free recall. Fifty-five normal elderly subjects and 28 patients with possible or probable AD were tested. The overall predictive accuracy of the DWR test was 95.2%. In addition, scores on the DWR test in normal subjects were not correlated with education or age. The inclusion of the DWR test in a previously studied cognitive detection battery for AD resulted in a considerable improvement in predictive accuracy