White Matter Injury Found to Be Preclinical Marker for Age-related Cognitive Decline

How to Interpret the Latest Data

BY MARK MORAN

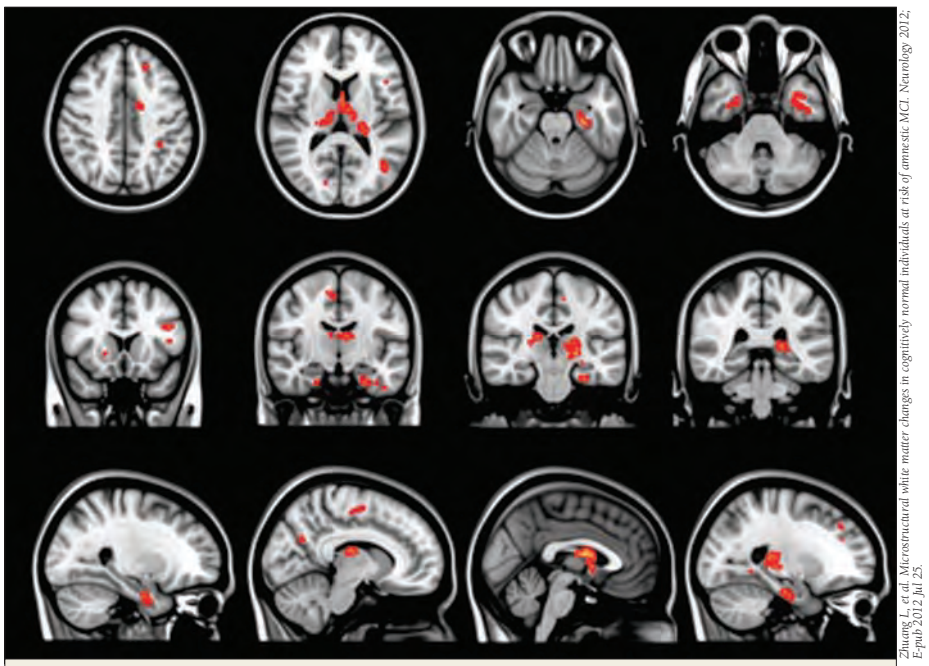
ARTICLE IN BRIEF

Experts discuss the clinical importance of three new papers that support the theory that early white matter injury may be a preclinical marker for age-related cognitive decline and for Alzheimer's disease.

Early white matter injury may be a preclinical marker for age-related cognitive decline and for Alzheimer's disease (AD), but the relationship between cognitive decline, white matter injury, and other neurodegenerative processes remains to be clarified.

Three separate studies appearing in the July 25 online edition of *Neurology* add weight to the argument, supported by previous research, that white matter lesions are complicit in the development of age-related cognitive impairment and AD.

The studies include a report by researchers at Oregon Health & Science University and the department of neurology at the Veterans Affairs Medical Center in Portland on the white matter hyperintensity (WMH) burden preceding mild cognitive Impairment (MCI); on microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI by researchers at the University of New South Wales; and on MRI-leukoaraiosis thresholds and the phenotypic expression of dementia by researchers at the University of Florida, the University of Illinois, and Drexel University.



Zhuang L, et al. Microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI. Neurology. 2012; Epub 2012 Jul 25.

LIN ZHUANG, PHD, and colleagues demonstrated here the pattern of fractional anisotropy (FA) reductions in presymptomatic individuals who eventually developed amnestic mild cognitive impairment. Voxels of significantly decreased FA are shown in red-yellow and overlaid on the template. Row 1 is an axial view (the left side of the image corresponds to the right hemisphere of the brain for the coronal and axial views); Row 2, is a coronal view; Row 3 is a sagittal view: the first two panels show the right side of the brain, the last panels show the left side.

Experts in neurodegeneration and cognitive impairment who reviewed the reports agree the three studies highlight in novel ways the role of white matter lesions in cognitive decline.

"White matter [injury] is now included in the discussion about the pathogenesis of dementia," Christopher Filley, MD, professor and chief of neurology at Denver VA Medical Center and interim director of the Alzheimer's Disease and Cognition Center, told *Neurology Today*. "Far from being a bystander, white matter may be a key component in the development of dementia, and white matter dysfunction as measured with modern neuroimaging has been repeatedly demonstrated in patients with many dementing disorders.

"These three papers all add to this literature, addressing the contributions of white matter dysfunction to models of incipient dementia in older people," he continued. "All three report new findings that illuminate early stages of the processes leading to late-life dementia."

MRI: WHITE MATTER HYPERINTENSITIES

For instance, the Oregon study on white matter hyperintensities (WMH) on MRI, found that the percentage of increased WMH volume occurred 10.6 years before the onset of mild cognitive

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TRAJECTORY OF WHITE MATTER HYPERINTENSITY BURDEN PRECEDING MILD COGNITIVE IMPAIRMENT

- 181 cognitively intact elderly volunteers underwent yearly evaluations, including brain MRI, and cognitive testing. MRI's were analyzed for imaging markers of neurodegeneration including white matter hyperintensities (WMH) and ventricular cerebrospinal fluid (vCSF) volumes.
- During a follow up duration of up to 19.6 years, 134 subjects converted to mild cognitive impairment (MCI).
- Acceleration in percentage WMH volume increase occurred 10.6 years before MCI onset.
- Out of sixty-three subjects who converted to MCI and had autopsy, only 28.5 percent had Alzheimer's disease (AD) as the sole etiology of their dementia, while almost just as many (24 percent) had both AD and significant ischemic cerebrovascular disease present.
- The study was supported in part by grants from the Department of Veterans Affairs, NIH, the Max Millis Fund for Neurological Research, the Storms Family Fund at the Oregon Community Foundation, and the T&J Meyer Family Foundation.

MICROSTRUCTURAL WM CHANGES IN COGNITIVELY NORMAL INDIVIDUALS AT RISK OF AMNESTIC MCI

- Structural MRI and diffusion tensor imaging were acquired at baseline to assess gray matter atrophy and microstructural white matter changes in 193 cognitively normal individuals, of whom 173 remained cognitively stable and 20 were diagnosed with amnestic MCI 2 years later.
- At baseline, compared with the cognitively stable group, amnestic MCI converters had substantial reductions in white matter integrity in the precuneus, parahippocampal cingulum, parahippocampal gyrus white matter, and the fornix.
- Other diffused white matter changes were observed in the frontal, parietal and subcortical regions, whereas gray matter structures were relatively intact.
- The fractional anisotropy (FA) values of the precuneus were found to be a predictor of conversion from cognitively normal to aMCI. In addition, the FA values of the left parahippocampal gyrus white matter were predictive of subsequent episodic memory decline.
- Funded by Australian National Health and Medical Research Council and Australian Research Council.

White Matter Injury, Alzheimer's Disease

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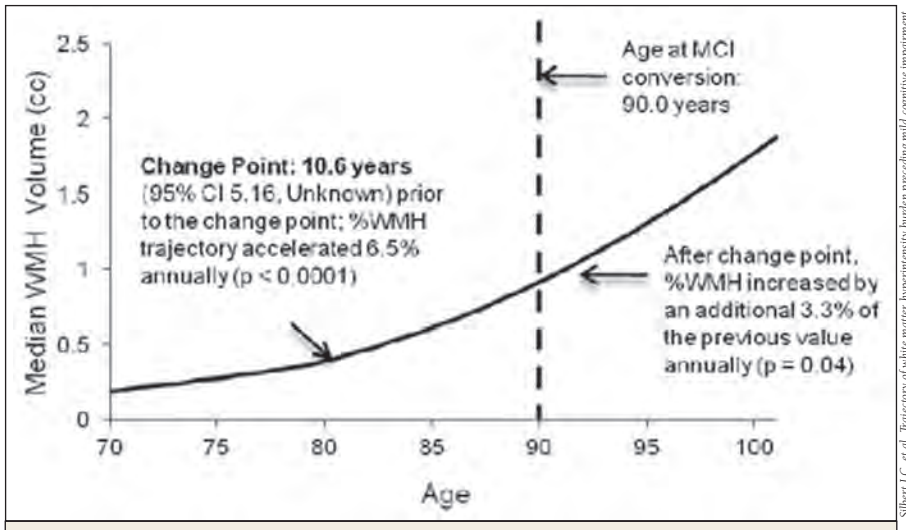
impairment (MCI) in a cohort of cognitively intact elderly volunteers who underwent yearly evaluations, including brain MRI, and cognitive testing.

"In the past, much of the imaging biomarker focus has been directed towards the cortex," lead author Lisa Silbert, MD, assistant professor of neurology, told *Neurology Today*. "Our study shows that there are changes in the white matter that occur many years before other structural brain changes are apparent. It indicates that the white matter in the brain is very sensitive to age-related pathologies associated with cognitive decline, and may be useful for the early detection of those at risk for cognitive impairment."

But reviewers for *Neurology Today* also agreed that all three studies raise questions requiring further research, including most prominently: Are white matter lesions directly causative of cognitive decline, or are they secondary effects of some other pathway to neurodegeneration?

"Observational studies are inevitably limited in their ability to say that an event is truly causal rather than an epiphenomenon of some other key pathway," Steven Greenberg, MD, PhD, the John J. Conway endowed chair in neurology at Harvard Medical School, told *Neurology Today*. "A further problem in analyzing white matter disease is that we don't know exactly what we're seeing on imaging — true infarction, chronic ischemia without infarction, or some type of non-ischemic injury. T2-hyperintensitities, and likely reduced fractional anisotropy as well, are clearly the nonspecific outcomes of multiple forms of brain injury. Not knowing exactly which type of injury we're looking at also means that we don't know whether some forms of white matter injury and not others are the actual contributors to cognitive dysfunction."



Silbert LC, et al. Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. Neurology 2012; E-pub 2012 Jul 25.

THE STUDY BY LISA SILBERT, MD, et al. shows the median white matter hyperintensity volume over time, using the results of the change point models and assuming MCI onset would occur at age 90 (mean age of MCI onset among the study cohort).

WHY DO WM INTENSITIES PROGRESS?

Acknowledging that the question cannot be answered by her own study, Dr. Silbert suggested that progression of white matter hyperintensities may be due to both vascular and Alzheimer's pathologies, possibly in a synergistic fashion.

"It is clear from many previous studies that age-related white matter hyperintensities are a sign of cerebrovascular injury and that progression of these lesions are associated with cognitive and motor decline and increased risk of conversion to cognitive impairment," she said. "There have also been several studies showing increased white matter change in those with Alzheimer's disease that was not explained by the presence of vascular risk factors.

"In our study, WMH burden accelerated 10.6 years prior to MCI conversion, a time frame consistent with a previously postulated temporal lag of approximately 10 years between the deposition of amyloid beta (Abeta) and the clinical syndrome of Alzheimer's disease. However, of the subjects from our study who eventually converted to Alzheimer's disease, less than half had Alzheimer's pathology as the sole etiology of their dementia, with just as many subjects having a significant amount of coexisting vascular pathology."

THE MESSAGE FOR CLINICIANS

Until the precise relationship between white matter injury and cognitive decline is clarified, what should neurologists treating patients at risk for cognitive impairment take away from the three *Neurology* studies?

At a minimum, Dr. Filley suggested that for neurologists treating patients with cognitive decline and other patients concerned about developing late-life cognitive dysfunction, "it seems reasonable to advise medical and lifestyle measures designed to protect white matter, as they may prove beneficial for helping prevent both vascular dementia and, conceivably, Alzheimer's disease."

Eric Smith, MD, assistant professor in the department of clinical neurosciences at the faculty of medicine at the University of Calgary, told *Neurology Today* that perhaps the most clinically relevant finding — from the study on MRI-leukoaraiosis thresholds and the phenotypic expression of dementia — is that lesions involving as little as 3 percent of the white matter produce impairment in working memory in demented persons. He noted that current guidelines from the American Heart Association/American Stroke Association recommend that there should be a "clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse subcortical cerebrovascular disease pathology" to diagnose probable vascular dementia.

"By identifying thresholds for severity the findings should help the clinician understand how much WM leukoaraiosis may be considered benign, versus how much might be considered sufficient to warrant a clinical diagnosis of probable or possible vascular dementia, or mixed dementia," Dr. Smith said. "Although volumetric assessments are not feasible in clinical practice, there are rating scales with acceptable inter-rater reliability that correlate well with quantitative assessments and are rapid enough to consider for clinical use."

But Dr. Smith added that a major barrier to better assessment of white matter lesions in clinical practice is the remarkable variability in terms, definitions, descriptions and thresholds for reporting them on clinical radiology reports.

"Clinical practice would be served well by the development of consensus standards for assessment and reporting of these common age-related lesions," he told *Neurology Today*. And he noted that a consensus group (of which he is a member) supported by the Centres of Excellence in Neurodegeneration, an international consortium, is currently working on such standards.

Finally, Dr. Greenberg said that the findings relating white matter injury to varying degrees and stages of cognitive decline suggest the heterogeneity of age-related cognitive impairment. "From a practical standpoint, it is time to stop thinking about age-related cognitive impairment as being primarily a single entity such as Alzheimer's disease or vascular dementia," Dr. Greenberg said. "Mixed neurodegenerative plus vascular pathologies appear to be the rule, not the exception.

"As clinicians, it is reasonable for us to actively control vascular risk factors in all our patients, and to actively support research trials aimed at teasing apart and treating the various contributors to the dementia epidemic." •

MRI-LEUKOARAIOSIS THRESHOLDS AND THE PHENOTYPIC EXPRESSION OF DEMENTIA

- A consecutive series of 83 individuals with insidious onset/progressive dementia clinically diagnosed with Alzheimer's disease (AD) or small vessel vascular dementia (VaD) completed neuropsychological measures assessing working memory, visuoconstruction, episodic memory, and language. A clinical MRI scan was used to quantify leukoaraiosis, total white matter, hippocampus, lacune, and intracranial volume.
- Leukoaraiosis explained a significant amount of variance in working memory performance when it involved 3% or more of the white matter with curve estimations showing the relationship to be non-linear in nature.
- Greater leukoaraiosis (13%) was implicated for impairment in visuoconstruction.
- Funded by the NINDS and the Alzheimer's Association.

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