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

How to Interpret the Latest Data

BY MARK MORAN

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.

**TRAJECOTRY OF WHITE MATTER HYPERINTENSITY BURDEN PRECEDING MILD COGNITIVE IMPAIRMENT**

- 181 cognitively intact elderly volunteers underwent yearly evaluations, including brain MRI, and cognitive testing. MRIs 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.

**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.
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improvement (MCI) in a cohort of cog- nitzitely intact elderly volunteers who underwent yearly evaluations, including brain MRI and cognitive testing.

“In the past, much of the imag- ing 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 these 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 epiphe- nomenon 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 imag- ing — true ischemic or chronic ischemia without infarction, or some type of non- ischemic injury. T2-hyperintensities, and likely reduced fractional anisotropy, are clearly the nonspecific out- come 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 mat- ter injury and not others are the actual contributors to cognitive dysfunction.”

WHY DO WM INTENSITIES PROGRESS?

Acknowledging that the question cannot be answered by her own study, Dr. Sil- bert suggested that progression of white matter hyperintensities may be due to both vascular and Alzheimer’s patholo- gies, possibly in a synergistic fashion.

“It is clear from many previous studies that age-related white matter hyperin- tensities 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 acceler- ated 10.6 years prior to MCI conver- sion, 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 epi- them 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 neurolo- gists treating patients at risk for cognitive impairment take away from the three Neurology studies?

At a minimum, Dr. Falley suggested that for neurologists treating patients with cognitive decline and other patients concerned about developing late-life cognitive dysfunction, “it seems reason- able to advise medical and lifestyle mea- sures 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 Uni- versity of Calgary, told Neurology Today that perhaps the most clinically relevant finding — from the study on MRI-leukoaraiosis thresholds and the pheno- typic 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/Ameri- can Stroke Association recommend that there should be a ‘clear relationship in the severity and pattern of cognitive impairment and the presence of dil- fuse subcortical cerebrovascular disease pathology’ to diagnose probable vascular dementia.

“By identifying thresholds for sever- ity the findings should help the clinician understand how much WM leukoarai- osis may be considered benign, versus how much might be considered suf- ficient 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, defini- tions, 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 Centers 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 fac- tors in all our patients, and to actively support research trials aimed at teasing apart and treating the various contribu- tors to the dementia epidemic.”

REFERENCES: