Multiple White Matter Hyperintense Lesions: A Non specific Finding. Or Not?

Evidence suggests that the location of WMHLS can provide clues to the cause of cognitive impairments, supporting diagnosis and improving treatment.

By Ronald Devere, MD

This MRI shows multiple white matter hyperintense lesions (WMHL) in subcortical and periventricular regions compatible with cerebral microvasular disease or a nonspecific finding. In view of patient’s age, and non-enhancing lesions, a demyelinating disorder is much less likely.” How many times have you seen this brain MRI report in your patients? You may have seen this report in patients with headache, seizures, or dizziness, or in patients with cognitive symptoms. The real question is how often these reported changes correlate with your clinical diagnosis in general and specifically in patients with cognitive impairment, including mild memory loss.

Unanswered Questions
A literature search reveals many articles that suggest a significant clinical correlation between WMHL and decreased performance on neuropsychological test results. This has also been described in future risk of mild cognitive impairment (MCI), and dementia. As such, important questions are:

a.) How does WMHL interfere with cognitive processing? and;

b.) Where should these lesions be located to explain the many different impairments that can occur with cognition?

As clinical neurologists, having the answers to both of these questions would be extremely helpful, by indicating which WMHL patterns are “benign” and which patterns point to different cognitive impairments. The answer to the first question has mainly been an hypothesis, not solid direct evidence. Nordahl et al in 2006 stated that they believed that WMHLS interfere with cognitive function by interfering with the speed of signal transmission in the affected regions. Answers to the second question had been based more on objective information. Different authors have postulated that clinical impairment due to WMHL should be associated with lesions in discrete areas involving white matter tracts connecting cortical networks serving clinical functions. Guttman et al in 2000 showed that WMHL in the occipital parietal periventricular regions correlated clinically with a gait disorder. O’Sullivan et al in 2005 showed that WMH stroke lesions in the frontal lobe were associated with executive dysfunction in CADASIL patients (cerebral autosomal dominant arteriopathy with stroke and ischemic leukoencephalopathy).

Smith E.E. et al 2011 published a very important paper that correlates WMH location using Diffusion Tensor Imaging (DTI) and cognitive impairment using neuropsychological testing. DTI is a radiology technique that measures the movement of water molecules in axons. The most commonly reported measure (fractional anisotrophy) expresses direction of water diffusion within fibre tracts. Another measurement in DTI is measuring the mean diffusion (MD) of water in the white
matter. Under normal circumstances, water movement in intact axons is limited and follows axonal walls. In axonal disruption for any cause, this water movement is disrupted.

The prospective study involved 147 patients who were 65 and older, had an informant for collateral history, and had no known dementia or major vascular risk factors (atrial fibrillation, insulin-dependent diabetes), stroke, or a diagnosed cognitive impairment from a medical disorder. A 22-item neuropsychological test was performed with the average time between MRI and neuropsychological testing being 76 days. Of the 147 patients in the study, 40 had normal cognition (CDR=0), 96 had MCI (CDR=.5), and 11 had dementia due to Alzheimer’s disease (CDR=1). This study had a high number of MCI patients.

Factors that were associated with higher number of WMHL on MRI were presence of hypertension, MCI, and dementia. Whole brain voxel-based analysis, accounting for age and years of education, was performed to determine relationship between WMHL frequency and neuropsychological score at each voxel. The study found that abnormal executive function on neuropsychological testing correlated with the frequency of WMHL in bilateral inferior frontal white matter; temporal occipital periventricular white matter in both hemispheres; right parietal periventricular white matter and anterior limb of internal capsule bilaterally. Abnormal episodic memory was associated with WMHL in right inferior temporal occipital region, left temporal occipital periventricular white matter, and anterior limb of internal capsule on the left. These findings strongly support the hypothesis, especially in MCI, that the WMHLs cause cognitive impairment by disrupting cortical connections mediated by specific white matter tracts. Unfortunately, no comment or data was mentioned in the study of the 40 subjects with normal cognition.

Previous studies have looked at much larger regions such as the entire frontal lobe or the periventricular region compared to the subcortical regions. Studying these larger brain areas leads to less clinical correlation because of involvement of multiple white matter tracts going to many destinations. Smith et al 2017 used the smallest regions of WMHL, controlled for total white matter volume, and had a much higher spatial resolution, resulting in a stronger correlation between WMHL frequency and specific cognitive dysfunction. The main limitation of this study was that specific white matter tracts travelling through the WMHL regions were not identified.

Correlations
What do we know about these white matter tracts in a premortem setting that can correlate between WMHL and cognitive impairment? Fortunately a number of studies have identified the white matter tracts of the normal human brain using diffusion tensor imaging along with track tracing studies in monkeys. One of the most thorough studies (by Catani and Thiebault de Schotten) produced an atlas of white matter tracts in vivo, using diffusion tensor imaging. Using this atlas and other studies, and correlating the information they gleaned from their WMHL study, Smith et al correlated their findings with the likely white matter tracts that were impaired. Table 1 summarizes some of the normal human white matter tracts and their function referenced in that study.

Based on all this information, Smith et al found those WMHL that were likely associated with impaired executive function involved the following fibre tracts: Uncinate fasciculus, inferior longitudinal fasciculus, frontal occipital fibres, superior longitudinal fasciculus, cingulum bundle, and anterior limb of internal capsule. The WMHL associated with impaired episodic memory in their study likely involved the following fibre tracts: frontal occipital tracts, inferior longitudinal fasciculus, rostral and caudal limbs of the cingulum bundle, and anterior limb and genu of the internal capsule.

More work needs to be done using more cognitively normal individuals and dementia cases. In this study, only episodic memory (memory storage) was tested. Encoding and retrieval parts of memory function were not specifically studied. As Smith
et al said; “These portions of memory could be involved in the same fibre tracts, but possibly others.” A very important concern that was not mentioned or evaluated in their study population was the presence of cortical vascular lesions and the possible presence of excess brain amyloid. The presence of one or both abnormalities could play a significant role in cognitive dysfunction. In the last number or years, we have seen the discovery that cortical lesions in multiple sclerosis, for example, become an important source of cognitive decline and are usually not seen in MRI scans of the brain with or without contrast. Diffusion Tensor Imaging is very valuable in evaluating white matter tract abnormalities, not gray matter pathology, except atrophy.

**WMHLs and Amyloid**

Up until the last four or five years, increased amyloid (a hallmark of Alzheimer’s) in the brain could only be certainly diagnosed post mortem. Amyloid can now be seen in vivo with a PET scan using Pittsburgh compound B. Other more user friendly agents like 18F Florbetapir and 18F-flutemetamol are being studied at this time. Gold et al autopsied 156 elderly individuals and studied the WMHL, other vascular lesions, cortical lesions, as well as amyloid and Tau pathology in their brains. They concluded that the clinical expression of vascular changes is dependent on lesion type and location (white matter and cortex), as well as severity of concomitant Alzheimer’s Disease related pathology. Lee et al recently did a study in Korea looking at WMHL and the presence of amyloid. Using PET scanning with Pittsburgh Compound B, they found many of their WMHL patients with negative amyloid in the brain and cognitive impairment, but the WMHL were very extensive and much more than reported in Smith’s study and overall higher than in any western study. This is very interesting, but more work, using amyloid PET scanning, needs to be done on many of these patients with various numbers of WMHL.

It may well turn out that many more individuals with pure WMHL and cognitive impairment will have a higher frequency of MCI and vascular dementia than previously recognized. This could turn out to be more “welcome” news to patients and their loved ones because “pure” vascular cognitive impairment may possibly be more easily modified with aggressive treatment of vascular risk factors and use of cholinesterase inhibitors than dementia in those individuals with a combination of AD plus a vascular cause or pure AD. This in turn could help decrease the public fear about getting AD, especially when memory loss occurs. In my experience, telling patients and caregivers that strokes and not AD are the cause of their loved one’s cognitive disorder often brings a big sigh of relief.

There have been a number of studies of vascular dementia treated with cholinesterase inhibitors and memantine (glutamate inhibitor) which have shown some improvement in behavior and activities of daily living and less cognitive decline. The criticism of these studies is that the possible presence of associated Alzheimer’s disease was not eliminated. Cerebral vascular dementia has been shown to have a worse survival than Alzheimer’s and worsens as the grade of cerebral vascular disease increases. This has been shown to be due to a combination of factors that include increased myocardial infarction, more physical disability of stroke dementia, and the presence of multiple ongoing risk factors, including hypertension, diabetes and high cholesterol. Diagnosing cognitive impairment due to primary vascular disease, being sure Alzheimer’s disease is not present, and aggressively treating vascular risk factors may turn out to arrest the disorder. Several large prospective studies of aggressive hypertension treatment have shown a significant risk reduction of dementia.

**What does this information suggest for the clinical neurologist?**

1. It helps to emphasize the importance of WMHL in explaining symptomatic cognitive complaints and impairment in many of our patients.

2. Neuroradiologists, in my experience, do not usually describe the locations of WMHL in any
Dementia Insights

**Table 1. Some Cerebral White Matter Tract Anatomy and Function**

<table>
<thead>
<tr>
<th>Name of Tract</th>
<th>Location and Connections</th>
<th>Function</th>
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<tbody>
<tr>
<td>Arcuate Fasciculus (AF)</td>
<td>Connects Perisylvian cortex of Frontal, Parietal and Temporal lobes</td>
<td>AF of left brain important in language and praxis. AF of right brain involved in visual spatial processing and language, such as prosody and semantic</td>
</tr>
<tr>
<td>Cingulum</td>
<td>Medial located bundle that runs in the Cingulated gyrus all around the Corpus callosum. Longest fibres run from Ant.Temporal gyrus to Orbital Frontal cortex. Short fibres connect Medial frontal, Parietal, Occipital &amp; Temporal lobes to Cingulum cortex</td>
<td>Part of limbic system. Important for attention, memory, emotions and behavior control</td>
</tr>
<tr>
<td>Inferior Longitudinal Fasciculus</td>
<td>Ventrally located. Connects Occipital and Temporal lobes. Long fibres connect visual areas to Amygdala and Hippocampus</td>
<td>Important for face recognition, visual perception, reading, and visual memory</td>
</tr>
<tr>
<td>Superior Longitudinal Fasciculus</td>
<td>Links Parietal and Temporal regions with Prefrontal cortex.</td>
<td>Important in spatial processing and spatial attention</td>
</tr>
<tr>
<td>Uncinate Fasciculus</td>
<td>Ventral in location; connects Anterior Temporal lobe with Medial &amp; Lateral Orbital Frontal cortex</td>
<td>Part of limbic system involves emotional, memory, and language processing</td>
</tr>
<tr>
<td>Inferior Frontal-occipital Fasciculus</td>
<td>Ventrally located; connects Ventral Occipital lobe and Orbital Frontal cortex</td>
<td>May participate in reading, attention, and visual processing</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>Connects Prefrontal cortex and Anterior Thalamic nuclei and Prepontine fibres to the Cerebellar Posterior lobe</td>
<td>Same as above</td>
</tr>
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detail. They usually say that they are present and likely suggest microvascular disease. Based on this new information about WMHL, neurologists need to educate radiologists so they can describe the exact locations of many of these lesions and/or review the details of these lesions ourselves.

3. Patients who come to see a neurologist for non-cognitive symptoms and turn out to have a number of WMHL on MRI or the equivalent on a CT scan of the brain, and the lesions are located in one or more regions, such as bilateral inferior frontal white matter, scattered frontal white matter clusters, left or right periventricular temporal occipital regions, or bilateral anterior limb or internal capsule, should perhaps undergo a thorough cognitive exam during the same or next office visit, which should include a cognitive history and collateral history along with an office cognitive test. (MMSE is not very sensitive in memory and executive function impairment). The Kokemen short test of mental status or Montreal Cognitive assessment test is much more sensitive for these parameters. A thorough history of all vascular risk factors should be obtained. If the patient and/or collateral history suggests cognitive dysfunction, and are supported by office testing, then neuropsychological testing should be considered for a more thorough and diagnostic evaluation. Knowing where the WMHL are located, and the results of the cognitive evaluation, a possible correlation can be made (e.g., amnestic mild cognitive impairment or MCI for executive dysfunction) and would highly suggest a vascular cause.

This kind of clinical example requires more study, but I believe it should be considered in clinical practice because of the possibility that many
of these patients may actually have cognitive impairment that has not been emphasized or addressed. If cognitive impairment is present, additional metabolic and vitamin studies should be done and an amyloid PET scan (when available) would be welcomed to help in determining the diagnosis, provided the patient and family are in agreement with this (if there is only MCI, a diagnosis of underlying AD may not be wanted). This amyloid scanning should be available in the very near future. This scan would hopefully reduce the need for other diagnostic tests like, SPECT, Glucose PET scanning and spinal fluid assessment for Beta amyloid and Tau. Aggressive treatment of vascular risk factors, exercise and cognitive stimulation, along with close follow up should be pursued.

4. Patients who come to see a neurologist with cognitive complaints will no doubt go through the usual cognitive evaluation. The presence of WMHL on MRI should not preclude other routine diagnostic tests for cognitive impairment, such as blood work (e.g., thyroid, B12, and folate) and neuropsychological testing. The WMHL locations should be correlated with cognitive testing and may well turn out to be the main cause of the cognitive impairment. An amyloid PET scan should be performed when available, provided the family and patient agree, to see if AD is present. The knowledge that WMHLS in certain brain locations are the cause or play a role in the patient’s cognitive impairment will increase diagnostic confidence, not just consider them a “non-specific finding” or unknown effect. Aggressive treatment of vascular risk factors, encouraging exercise, and cognitive stimulation should be stressed.

Conclusion
This article discusses the clinical importance and location of WMHLS. Diffusion tensor imaging, which is not available as yet for standard everyday clinical use, has allowed an in vivo dissection of the white matter tracts of the normal and pathological brain, and helps to correlate some of the white matter lesions with impaired cognitive function. This concept will need the help of our neuroradiology colleagues to specifically state in their MRI/CAT scan reports exactly where these WMHLS are located (not frequently done) and/or require us to be more diligent in reviewing our patient’s scans. This, along with future specific amyloid imaging (currently being aggressively studied and likely to reduce the need for SPECT, Glucose PET scan and spinal fluid amyloid and Tau levels) will give us a more accurate in vivo diagnosis of pure Alzheimer’s, mixed, or a pure vascular cause. This technology will be very welcome, because it will help solidify the role and frequency which WMHLS plays in cognitive impairment. Treatment trials using cholinesterase and glutamate inhibitors along with aggressive treatment of vascular risk factors in the “pure” vascular causes are needed.

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