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2006 SOA LTC Conference Talk: White Matter Lesions

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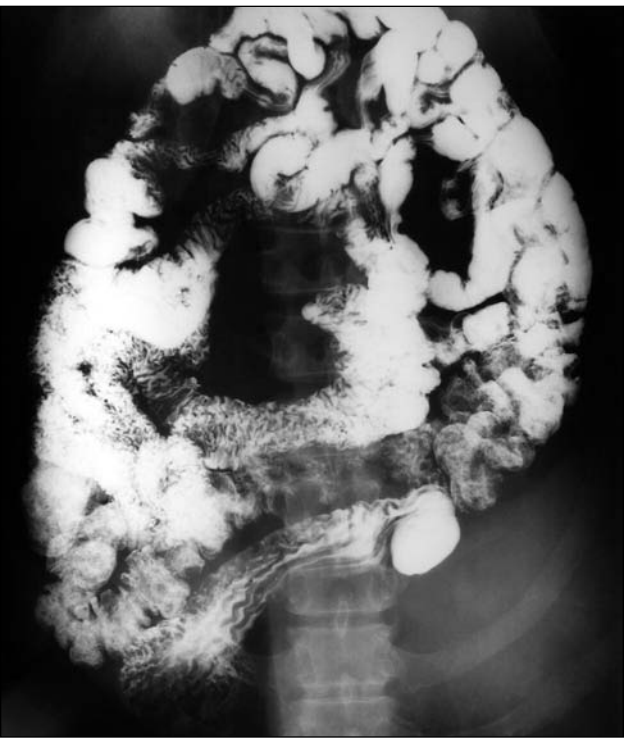

The abnormalities we now call white matter lesions (WML) were initially identified in people's brains approximately 25 years ago with the advent of CT scanning. At the time they were called "leukoaraiosis," which means low density of white matter, because that was their appearance on a CT scan. When MRIs became the dominant mode of brain scanning, several new descriptive terms for them emerged, including "white matter hyperintensities" and "unidentified bright objects" (UBOs), both of which refer to the fact that the T2 spin portion of the scan makes the lesions look whiter than normally myelinated tissue, despite the fact that the areas themselves are actually demyelinated on direct pathological inspection.

The major reason for our interest in WML from an LTC perspective is that their presence is associated with an increased risk of stroke and dementia.

What WML Are

The natural starting point for a discussion of white matter lesions is the white matter, which lies beneath the gray matter of the cortex or outer layer of brain tissue. It is white because it is made up largely of neurons covered with myelin that are transmitting signals from the cells of the gray matter.

If you look at a white matter lesion under the microscope, you see loss of myelin and glial rarefaction, or a decrease in the supporting structure cells in that part of the brain.

It appears less white than surrounding tissue to the naked eye, even though it looks whiter on the T2 spin images of a brain MRI. WML look different from strokes on an MRI and also look different under the microscope, in that strokes appear as

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scar tissue or, in some cases, an actual hole in white or gray matter.

What Causes Them

The generally accepted cause of the demyelination is ischemia due to decreased blood flow in the small arterioles, which, in turn, is caused by hyaline thickening of the walls of the arterioles. The larger question is why this damage occurs in some people's brains but not in others.

All studies done on WML causation have found two major correlates: hypertension and aging. Both the likelihood & severity of WML correlate not only with whether hypertension is present, but how long it has been present and how well it is controlled. For example, the Atherosclerosis Risk in Communities (ARIC) study, which is one of the few high quality studies that has been done on WML, has found that people aged 55-72 with well-controlled hypertension have about twice the incidence of severe WML as people without hypertension. Meanwhile, people with uncontrolled hypertension have about triple the incidence.

Age is an even stronger correlate than hypertension with regard to both the presence and severity of WML.

Age is an even stronger correlate than hypertension with regard to both the presence and severity of WML. For people with no hypertension, the prevalence of severe WML increases with each decade, such that after the age of 80, nearly half of all people have severe WML. Meanwhile, about half of all normotensives have at least mild WML on their MRIs, which is basically the same as for people with well-controlled hypertension.

Simply saying that age is the dominant cause of WML is not a completely satisfying explanation, given that people develop different degrees of them at different ages. There are other lesser factors that show some correlation such as APOE4 status, and chronic hypoxemia, but there are other factors yet to be worked out and these almost certainly include genetic susceptibility factors.

Curiously, unlike the case with atherosclerotic cerebrovascular disease, the role of the other recognized cardiovascular risk in WML development is surprisingly limited. Diabetes and hyperlipidemia play no part. The role of smoking is a bit controversial: findings vary from one study to another, and depending on the study, it either does cause WML, but only in African Americans; it doesn't cause, but just worsens WML once it is already present; or no, smoking has no effect.

The Importance of WML Severity and Location

For gauging WML severity, the most commonly used grading system is a system that starts at zero for no white matter lesions and then grades up to 9, the most severe level. Each successive grade is oriented to the severity of the lesions in both the subcortical and periventricular areas. Thus, grade 1 WML means there is no continuous lesion rim around the ventricles AND the subcortical lesions are dots. Grade 2 is the next step up with a continuous periventricular rim plus patches of WML as opposed to dots. The grades increase until by grade 8, in which the lesions come pretty close to involving pretty much the entire white matter of the brain, then grade 9 is even worse than that.

The Rotterdam variation of this system recognizes the fact that periventricular lesions have special risk implications independent from subcortical WML severity and therefore grades the periventricular and subcortical lesion severity separately.

For underwriting risk assessment purposes, it is more practical to think in terms of mild, moderate and severe WML, in part because that is how a radiologist would normally present the grade in a report. In such a system, grade 1 with its subcortical dots translates as mild; grade 2 with its subcortical patches and a thin rim translates a moderate; and everything else is severe.

WML and Stroke Risk

The Cardiovascular Health study examined the relation of WML grade with annual clinical stroke risk in the elderly. It found that severe WML—defined as anything grade 3 and up—predicts a 2.4 to 3.7- fold risk of stroke compared to mild or no WML, independent of other factors.

The Rotterdam Scan Study took their analysis a step further and discovered that it is the severity of the periventricular lesions that is the main correlate of stroke risk. You can actually have a heavy burden of subcortical dots and patches with a less than a 50-percent increase in stroke risk if you don't have periventricular lesions.

It is also important to note that presence of both severe WML and a silent stroke on an MRI are strong predictors that present basically additive risks for a future stroke.

WML & Dementia Risk

WML is a manifestation of small vessel disease of the brain, and small vessel disease is both implicated in vascular dementia and known to amplify the pathologic changes of Alzheimer's disease. It makes sense that presence of severe WML would represent an increased risk of dementia. The most interesting thing about that though is that it is mainly the presence of severe periventricular WML that is the big risk.

The Rotterdam study did demonstrate a two-fold risk for severe subcortical lesions—the dots and patches—as well, but this did not reach statistical significance. In contrast, in people with severe periventricular lesions, not only is cognitive decline much more likely, but it also progresses faster.

Not just the presence of WML also evidence of its worsening on successive MRIs correlates with a greater likelihood of cognitive decline.

The presence of both WML and cortical atrophy predict a higher likelihood of cognitive decline following a stroke. In fact both seem to be more predictive than the size of the stroke.

WML & Migraines

Definitive studies have yet to be done to help sort out the true association of migraine as a risk for WML. One of the problems is that mild WML are so common in people both with and without migraines that it is hard to tease out a true relationship with regard to severe WML. One reasonably well-done study has found that severe subcortical WML were somewhat more frequent in women with migraines but not men. And they were somewhat more frequent in women with high-frequency migraines.

In any event, to the extent WML may be caused or exacerbated by a migraine hx, there is no good evidence that they increase stroke or cognitive impairment risk We need better studies to sort this all out.

It is also noteworthy to mention that small, silent posterior strokes are more common with migraines, especially in people who have auras.

Underwriting WML

An optimal rating system for LTC risk considers all of the following: overall severity periventricular lesion severity, associated symptomatology, age, hypertension presence and control, coexistent lacunar or other infarct(s), cerebral atrophy presence and severity, and WML stability.

In general, the finding of mild WML is not a concern.

Moderate WML are not a concern if an isolated problem at older ages, especially if it's just some subcortical patches. However, it is more of a rating concern in younger ages, especially if there's moderate periventricular rim involvement, and/or progressive or combined with hypertension not well controlled and/or if combined with moderate or worse cerebral atrophy and/or lacunar or other infracts.

Severe WML is a major risk concern at younger ages and can also be a major concern at older ages, especially if it is periventricular and/or progressive or combined with hypertension not under excellent control and/or combined with moderate to severe cerebral atrophy or with stroke(s). ❋

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