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Cerebral Microbleeds and White Matter Disease: Separated at Birth?

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The evolving understanding of cerebral microbleeds represents one of the most important and intriguing developments in the field of cerebrovascular disease. It seems difficult to overstate the significance of the findings that beginning at age 60, roughly 20% of the population shows evidence of small, focal areas of brain bleeding. By age 80, that prevalence is nearly 40% (1). As impressive as those numbers may be, they may well represent an *underestimation* of microbleed prevalence. This is because the prevalence data are based on MR gradient echo sequences using field strength of 1.5 Tesla. Usage of the more sensitive susceptibility weighted imaging (SWI) along with 3 Tesla MR may show even more robust prevalence (2).

MR demonstrates microbleeds by imaging hemosiderin, and therefore what is demonstrated is the consequence, or signature, of the bleeding rather than actual hemorrhage. Pathological studies of microbleeds are relatively scarce, but the current consensus view is that hemorrhage at the level of small arteries and arterioles are the vascular substrate of what is imaged by MR (3). Nevertheless, microscopic hemorrhage in the aging brain appears to be vastly more prevalent than what is suggested by MR, with the overwhelming majority of subjects aged 70 and older showing evidence of hemorrhage at the capillary level (4,5). The relationship between these capillary hemorrhages and the lesions imaged by MR is uncertain, and is an issue of substantial significance.

Cerebral white matter disease is the other highly prevalent and relatively underexplored brain aging process closely linked to cerebrovascular disease. Prevalence of cerebral white matter disease is very high, with more than 95% of the population age 65 and older showing at least some white matter changes on MRI (6). However, “only” about one-third of this population show brain changes that appear to be substantial and may qualify as “white matter disease”(6). It is well known that classic vascular risk factors (especially hypertension) are closely linked to cerebral white disease (6).

In the current issue of European Journal of Neurology, Yamada and colleagues report a substantial association between presence of cerebral microbleeds and cerebral white matter disease (7). Both cerebral microbleeds and white matter disease are understood to be a manifestation of brain aging. However, in this study white matter disease was a better predictor of microbleeds, compared to patient age.

The observed association between cerebral microbleeds and white matter disease immediately raises questions regarding linkage between the two entities. Specifically, might there be a common underlying mechanism for both cerebral microbleeds and white matter disease? This is, of course, a difficult but important question.

There are several intriguing lines of evidence suggesting commonality for both cerebral microbleeds and white matter disease. As noted above, microvascular hemorrhages are highly prevalent in the aging brain (4,5). Presence of these capillary hemorrhages are

consistent with alterations of the blood-brain barrier, allowing for red blood cells to escape the microvasculature. Such a blood-brain barrier alteration could be transient or persistent.

Mechanisms underlying cerebral white matter disease have proven elusive. Aside from the already noted association with vascular risk factors, careful pathological study has demonstrated that microvascular alterations may be the best predictor of white matter disease as seen on MRI (8). Therefore, a microvascular origin might underly both cerebral microbleeds and cerebral white matter disease.

This is, however, a speculative scenario for a number of reasons. First, the relationship between brain capillary microscopic hemorrhages and the MRI-demonstrable cerebral microbleeds remains to be established. Second, a microvascular origin for cerebral white matter disease requires substantial confirmation by additional studies. Finally, and perhaps most provocatively, cerebral microbleeds and white matter disease could be linked by a completely different mechanism. For example, oligodendrocytes are known to be the principal iron storage site in the adult brain (9). Age-related degenerative changes in oligodendrocytes (presenting as cerebral white matter disease) could result in release of substantial quantities of iron into parenchyma. Could release of brain iron stores generate hemosiderin? This is contrary to traditional pathological views, but is a testable hypothesis. If so, release of stored iron could evolve into hemosiderin that gives the appearance of microbleeds. In other words, the hemosiderin signature of “microbleeds” could conceivably represent a non-hemorrhagic process.

All this, of course, makes for interesting armchair speculation. It is safe to say that the coming decade will shed some fascinating light on the topic during the exploration of a pathophysiologic link between cerebral microbleeds and white matter disease.

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