Sick arteries give their small cousins a beating: new insight into vascular pathology in Alzheimer's disease

That the brain's blood vessels, a.k.a. cerebrovasculature, play an important role in Alzheimer's disease (AD) and related brain disorders is not entirely new. In fact, it was Alois Alzheimer and some of his contemporaries who observed gross changes in the cerebrovasculature in AD already more than a century ago. Nevertheless, it is only since more recent years that the impact of cerebrovascular pathology on AD is becoming clearer.

As with any disease, knowledge of what happens before the disease starts is essential for finding therapies that may cure or at least halt AD. One of the important findings in AD research has been that blood flow to the brain is already reduced at early, pre-AD stages, indicative of not only reduced neuronal activity (i.e., less demand for oxygen and other nutrients) but also of pathologic changes in the brain's blood vessels. So far, most research has focused on these pathologic vessel changes in brains from subjects with full-blown AD, and then mainly on the microvessels as these show strong pathology in the disease. What is happening to these microvessels and their big cousins the arteries before AD kicks in, is, however, not much explored.

Therefore, in this study, we investigated changes in brain microvessels and arteries at the different neurodegenerative stages that precede and might lead to AD. We specifically looked at changes in three components of the vessel wall that are important for blood flow to and in the brain: elastin, smooth muscle cells, and collagen. Surprisingly, we found that the arteries in the brains of subjects with mild to moderate signs of neurodegeneration already showed loss of elastin and smooth muscle cells, a time point long before one can even speak of AD. The microvessels, on the other hand, only showed smooth muscle cell loss (they do not contain elastin) in the AD brains. The other main finding was that the arterial impairment followed the increase in the severity and brain distribution of so-called neurofibrillary tangles that are caused by misfolding of a protein called tau, which is part of the neurodegeneration process, and not of that of amyloid beta, another protein mainly related to AD. Again, the opposite was found for the microvessels: mainly amyloid beta seemed to affect them, not tau.

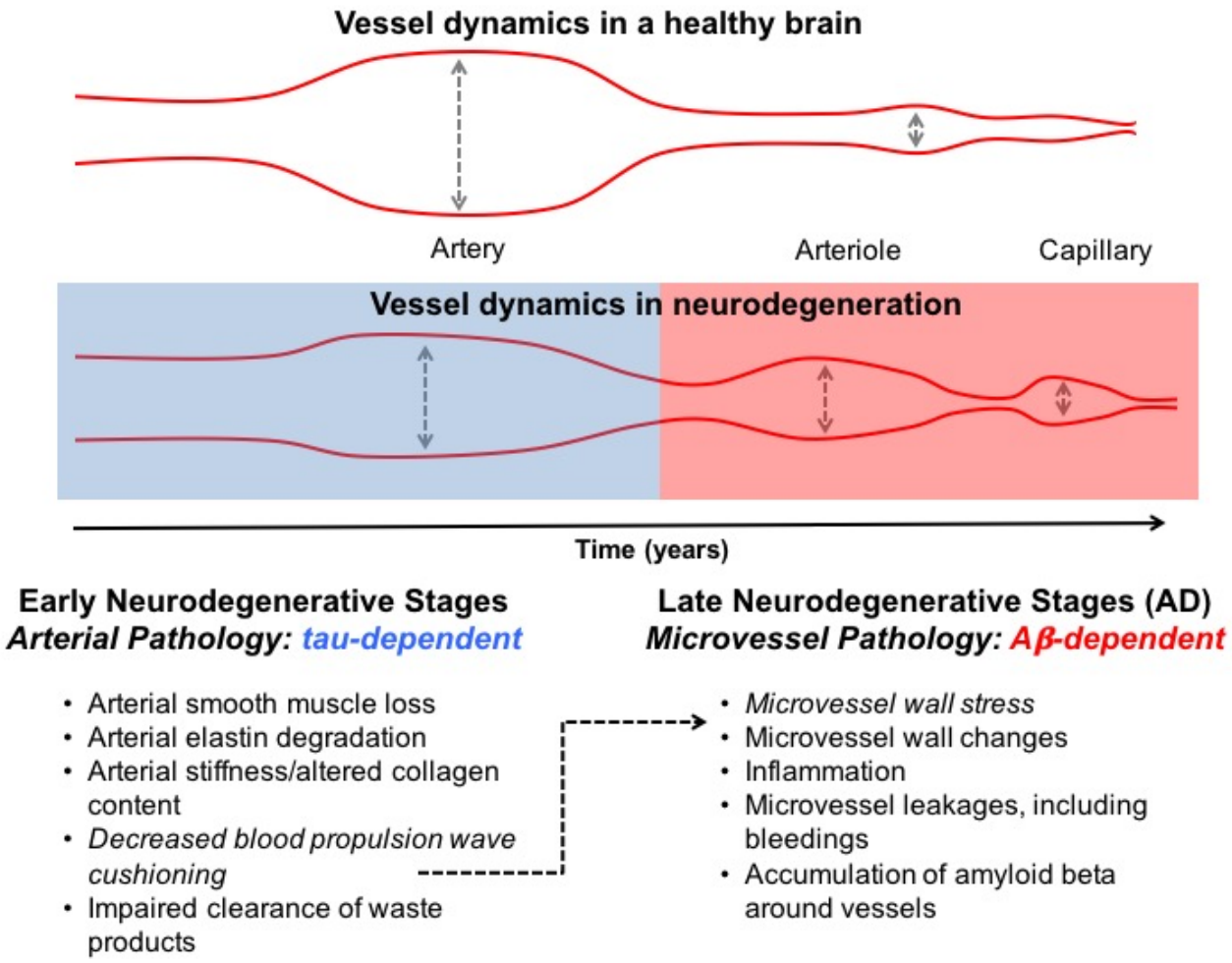

Fig. 1.

Why does such discrepancy exist between the arteries and the microvessels, and what is the importance of this finding for AD? Although the data from this study cannot provide a full explanation, the anatomy and wiring of the vasculature give important clues. As explained in Figure 1, arterioles and capillaries (the microvessels) are downstream of arteries. The arteries absorb most of the big pulsation waves that are sent through the vascular system by the beating of the heart, thereby protecting the relatively fragile microvessel wall from being too much extended. Further, this arterial mechanism is also important for the removal of all kinds of waste products produced by brain activity, thereby keeping the brain clean and clear of toxic waste accumulation. Thus, when arteries lose their capacity to adequately absorb these pulsation waves because of vessel wall pathology as we found in this study, the microvessels will be much more exposed to the beating waves, and one of the brain's main waste clearance routes will be compromised. Over time, this will lead to (pathologic) changes in both the microvascular wall to accommodate for the increased stress and in the brain environment, which then result in several downstream processes

negatively affecting the brain (Fig. 1). Although more research is required to find the precise underlying mechanisms, therapeutic targeting of the cerebrovasculature—especially the brain's arteries—may be beneficial in AD.

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