Editorial

Leukoaraiosis and Ischemia

Beyond the Myth

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Although Alois Alzheimer had described in 1902 a baffling extensive and severe degeneration of the cerebral white matter (misnamedBinswanger disease), over half a century of regular examination of brains by histological techniques failed to recognize the common occurrence of bilateral, patchy or confluent, white matter lesions revealed first as hypodense areas by computed tomography and later with much improved definition as hyperintensities in T2 and FLAIR sequences in magnetic resonance. Even in retrospect, it is hard to identify on histological sections the exact location of lesions so brightly demonstrated on magnetic resonance images. The name leukoaraiosis will be used in this editorial to designate these white matter lesions, as opposed to others related to demyelinating, infectious, toxic, or metabolic processes.

Having named the finding we were left with an existentialist lesion in search of significance. As a marker, leukoaraiosis is a prognostic factor for stroke and myocardial infarction. Its consequences, even in samples restricted to nondisabled elderly, include impaired cognitive function, as well as reduced motor function, and possibly late onset-depression.

But how are the lesions produced? Epidemiological studies suggest association with aging and vascular risk factors such as hypertension and diabetes, whereas histological studies indicate association with arteriolosclerosis of small blood vessels in the brain, consisting of replacement of mural smooth muscle by fibrohyaline material which eventually results in thickening of the wall and sometimes narrowing of the lumen. Several mechanisms are consistent with these findings: certainly ischemia–insufficient oxygen and nutrient delivery– is a possibility, but credible alternatives include alterations of the blood–brain barrier permeability either during hypertensive episodes or in relation to impaired venous return in the deep white matter. This would lead to vasogenic edema and leakage of molecules toxic to axons and their associated cells. Even disturbances in the circulation of cerebrospinal fluid could be involved. Depressed regional cerebral blood flow and acetazolamide reactivity has been shown in white matter hyperintensities, but it has proven difficult to demonstrate reduced regional cerebral blood flow combined with increased extraction fraction, which would constitute the imaging proof of ischemia. The term “incomplete infarct” does not advance our understanding of the process: it provides no more than a tattered cloak to hide the shame of our naked ignorance.

No animal model of leukoaraiosis is available. This is a common problem. Humans are often the only species to suffer a disease, and the range of ethical experimentation is very limited as compared with animals. Fernando et al have bridged the gap by taking brains from autopsies of demented and nondemented elderly donors, and treating them in parallel with both patients in whom magnetic resonance identifies the lesions, and laboratory animals in which immunohistochemically detected markers can be related to experimentally induced ischemia. Specifically the hypoxia-inducible factors HIF1α and HIF2α, as well as the candidate markers of hypoxia proteins neuroglobin and MMP7 are expressed in glial cells in deep subcortical white matter lesions at a significantly higher level than in normal white matter. The cellular distribution is worth mentioning, as these markers are overexpressed in astrocytes and microglia, but apparently not in oligodendrocytes. The correlation of hypoxia markers in the lesions with amyloid angiopathy load strongly suggest that when present the latter is also involved in the genesis of leukoaraiosis, despite affecting leptomeningeal and cortical blood vessels, in contrast to the basal ganglionic and white matter preference of arteriolosclerosis.

Leukoaraiosis may have a different etiology in periventricular white matter given that only one of the markers of hypoxia studied was increased in lesions in this area. On the other hand, denudation of the lining of the ventricles was more common in cases with periventricular, but not deep white matter lesions, suggesting that fluid accumulation associated with disruption of the ependyma is involved in the genesis of the former.

The article convincingly demonstrates that leukoaraiosis is associated with persistent tissular ischemia. Several questions remain in relation both to the effects and the genesis of ischemia.

Yes, ischemia is involved, but how does it produce the observed lesions? We do not even know which of the 3 ultrastructural substrates observed in experimental ischemia (swollen astrocytic processes, separation of myelin from axolemma, and enlarged extracellular spaces) is responsible for the histological appearance of rarefaction in human leukoaraiosis. The microglial activation demonstrated in the
lesions points to inflammatory cytokines as possible mediators of the effects of ischemia on tissue. What is the contribution of alternative mechanisms, such as disruption of the blood–brain barrier, a process suggested by the presence of plasma proteins in clasmatodendritic astrocytes? It is even possible that ischemia is secondary to alterations in blood–brain barrier permeability.

Information on the detailed time scale of development of single lesions in leukoaraiosis would provide an important clue to the previous question, but this intelligence is missing, despite the many population studies detailing progression of leukoaraiosis over a period of years. Full development of a stable lesion over a few days would be expected if ischemia is the primary factor. In that case, would a prolonged period of marginal oxygen delivery before a sudden drop in perfusion pressure be relevant? Ischemic preconditioning, the increased resistance to ischemia after subthreshold ischemic insults, documented in animal and human brain, is associated with expression of HIF1α, the protein Fernado et al found in deep subcortical leukoaraiosis. It may be worthwhile investigating whether leukoaraiosis could be explained as a manifestation of the ischemic preconditioning phenomenon. Finally, what triggers ischemia? Is it a failure of cerebral blood flow autoregulation, or simple narrowing of the vascular lumen? Are microemboli or microthrombi involved? What is the importance of endothelial and hemostatic activation? Although the Fernado et al study was not focused on these issues, they demonstrate vascular endothelial activation, but absent reduction of the diameter of the lumen.

Leukoaraiosis remains one of the most accessible markers of the pouting aging and vascular risk factors inflict on the brain. It is likely that the further dissection of its causes and consequences will reveal basic mechanisms of the processes that steal the cerebral function of so many of our elders.

References

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