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Vascular Burden of the White Matter

ARNE BRUN

ABSTRACT. In cerebrovascular disease of all kinds, the white matter bears a heavy burden—particularly in the early and late periods of life. The infarcts are of the complete and incomplete type, the latter accompanying and extending the white-matter damage of the former. Complete infarcts are mainly caused by vascular occlusions. Incomplete infarcts are mainly due to hypoperfusion, wherein pathogenic factors are, above all, different types of angiopathies leading to an inadequate autoregulatory response in the event of an episodic or more longstanding hypotension, acting as an etiological factor through hypoperfusion. There is growing consensus that white-matter lesions affect brain function. Correlation with symptoms and understanding of mechanisms behind the lesions would gain from more precise diagnostics as to tracts involved.

KEYWORDS: Brain; white matter; cerebrovascular disease; incomplete infarcts; hypotension; hypoperfusion

Since the seventies, when our neuropathological search for white-matter lesions and their cause began, the literature in the field has exploded, mainly based on new imaging methods but with few studies correlating the underlying pathology. MRI has thus come to set the standard, resulting in a nomenclature that may seem confusing: the intermediate white matter is called “the deep,” and the deepest portions are called periventricular. The subject is further clarified by Englund, together with a survey of the white matter pathology (Englund, 2000). Makris and colleagues (1999) show more precisely

the anatomy of different white matter tracts with an MRI-based topographic parcellation method.

The first level, the u-fibers or subcortical fibers, have received scant attention but are less prone to damage, probably due to their better and more direct and short vessel supply. The intermediate and deep strata are susceptible to flow disturbances, since they are supplied by long arteriolar penetrants, with blood pressure falling along the long supply line, and since they lack shunts and are scarce compared to the cortical supply. There may also be a difference in vascular density

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between strata “border zones.” Better known radial borderzones exist between the main cerebral arteries—not only in the cortex but also along their deep course towards the ventricular system. De Reuk (2000) points out that the relatively low flow and the high oxygen extraction in the white matter speaks for high oxygen dependency and sensitivity to ischemia.

RESULTS AND DISCUSSION

Forty years of neuropathological experience, including a large prospective dementia study (Brun et al., 1993), have shown that vascular dementia accounts for 25% of the cases, to which can be added a considerable number of cases with incomplete white-matter infarctions, particularly in Alzheimer’s disease (AD) (Brun et al., 1986). The study was made on whole brain coronal semi-serial sections, allowing a mapping of topography, extent, and regional severity of the lesions, and their clinical relevance could be evaluated through correlation with the symptomatology.

Against this background, the impression was gained that vascular lesions are rarely limited to the cortical grey matter but sometimes are limited to the central grey nuclear structures. The addition of selective white-matter lesions underscores the vascular burden of the white matter. Changes here are by Hachinski named *leukoaraiosis*, an unspecified clinical-radiological brain-imaging term that includes white-matter lesions (WML) and WMH. They are most likely dominated by ischemic complete and incomplete infarcts as defined structurally but include also areas of edema not representing true lesions and are here simply called WML.

Based on these experiences, we initially classified vascular dementia on neuropathological grounds in 1988; this was later revised in 2000 (Brun, 2000). In large vessel dementia, both cortex and subjacent white matter are regularly involved in the infarction, which centrally is complete but is surrounded by a large area of incomplete infarction in the white matter, undermining undamaged adjacent cortex. Strategic infarcts may be limited to grey matter, particularly in the central grey structures. In small-vessel disease with dementia, brain stem and central grey structures are involved but also and often to a greater extent the white matter especially frontally, showing lacunar complete infarcts surrounded by wide areas of incomplete infarcts (Brun et al., 1992). This is the case in Binswanger’s disease, one of the largest forms of small vessel dementia in our material. CADASIL is a rare example of widespread white-matter infarction of a similar type. Lastly, in hypoperfusive dementia, the white matter selectively suffers widespread incomplete infarcts, varying in severity from mild to severe short of complete infarction.

The white matter would be expected to suffer with the same frequency in nondemented vascular cases. Here, the more or less normally aged is a special large group in which white matter lesions are very common. An MRI population-based study showed a frequency that increased with age, at 80-90 years of age, leaving only a few percent entirely free of WML (deLeeuw, 2001). Nondemented individuals with WML perform worse on cognitive tests than do those without (Breteler, 2000). When pronounced, WML cause or assist in precipitating dementia. Also, others are of the opinion that WML are likely to

impair cognition, in particular as to speed, and then more due to periventricular than to deep lesions (e.g., Cees de Groot et al., 2000).

The frequency of WML in pathological studies is most certainly severely underrated. The complete infarcts are readily detected, but the incomplete ones, though large, may often go undetected on gross inspection and may be missed on small-sample microscopy. Whole brain routine sections then often reveal a surprising amount and frequency of incomplete infarcts if staining for myelin and axons is used. A parallel is drawn by Evangelo (2000) for normal appearing areas of white matter in MS, wherein special methods reveal a significant loss of axons, something attributed to lesions elsewhere. This goes also for milder hard-to-detect grades of incomplete infarction, which are corroborated by axonal counts (Englund et al., 1990). More advanced damage is diagnosed already on the combination of some degree of demyelination and a vital tissue reaction with partial loss of oligodendroglial cells, mild astrocytic gliosis, and sparse macrophages.

What, then, are the causes of WML? The complete infarcts are mainly caused by intracranial vascular occlusions due to hypertensive angiopathy. Extracranial stenoses or occlusions such as in the carotid artery may also lie behind such damage but also cause incomplete infarction. Thus, carotid stenosis, combined with hypotensive episodes, lead to border-zone infarcts, which may be incomplete and may even selectively involve the white matter in the deep-border zones. DeLeeuw and colleagues (2000) found a correlation between carotid sclerosis and periventricular WML on MR, but not that clearly to deep

WML. Tanoi and associates (2000) state that in Binswanger's disease, the essential mechanism behind diffuse myelin loss of the white matter is the dysfunction of the blood-flow regulation due to increased arterial stiffness caused by hypertensive vascular changes.

These and other situations with WML but without vascular occlusions indicate the importance of hypoperfusion as one cause of WML. Hypertension is a pathogenic mechanism that leads to occlusions and complete infarcts but also causes narrowing or wall stiffening, impairing the autoregulation and leading to hypoperfusion and incomplete infarcts. In 1986, Brun and colleagues proposed that episodic hypotension of various origin combined with fibrohyaline arteriosclerosis may be another, etiologic mechanism for incomplete infarcts. Particularly if succeeding hypertension, a hypotension that develops during the course of the dementia or in the senile period with its arteriolosclerosis of the aged might cause lesions through temporarily critically low flow levels, a principle since elaborated on by several authors.

Opinions on the importance of hyper- vs. hypotension are thus divided. Vermeulen and colleagues (2000) point out that several control studies were unable to confirm a correlation of hypertension to WML and found an association with hypotension. Pantoni and colleagues (1997) concluded that some types of leukoaraiosis were caused by ischemic injury due to altered autoregulation from arteriolar changes combined with repeated flow drops, resulting in incomplete infarcts. Sawada and colleagues (2000) found no correlation between WML and apoe 4, nor with CAA, and concluded that orthostatic hypotension may produce repetitive ischemia in the white matter,

especially in the elderly. Breteler (2000) expresses a similar opinion. According to DeCarli and associates (1999), "Altered auto regulation may explain how WML can occur in aging and in the presence of nonocclusive CVA as in amyloid angiopathy," and loss of autoregulation in orthostatism was a significant predictor of the extent of the WML. Hypotension is also a sequel of treatment for hypertension or with other drugs influencing the BP, which is why it is important to balance BP management, since acute BP reductions can become devastating.

A link between AD and cerebrovascular disease, especially of the white matter, may be capillary degeneration in AD, leading to metabolic derangement (Farkas et al., 2000; de la Torre, 2000). Aging and AD also show fibrohyaline arteriosclerosis that may lead to an impaired autoregulation; and amyloid angiopathy of the penetrator shaft may be another cause of vessel dysregulation. In these situations, hypotension—especially with orthostatic episodes—may act as an etiologic factor leading to hypoperfusion and WML!

The importance of hypotension for white-matter lesions associated with dementia has recently received strong support from a study by Zuccala and colleagues (2001) on 13,635 aged people. Twenty-five percent of those with heart failure and systolic hypotension showed cognitive impairment, the systolic hypotension being selectively associated with cognitive impairment.

FUTURE DIAGNOSTICS

Much obviously remains to be learned about the etiology and clinical expressions of WML. Future studies should include correlated extended neuropatho-

logical and refined brain imaging analyses. The MRI method described by Makris (1999) may prove a valuable method for topographic diagnostics of WML and for a correlation with symptomatology. The latter task appears to be particularly difficult in view of the fact that a lesion may affect several tracts and thus, secondarily, widely different cortical areas, with complex functional consequences.

Previous white-matter flow studies have usually produced only relative values or absolute values with limited resolution. Tsourio and colleagues (2001) measured white-matter flow velocity by transcranial Doppler and found WML to be associated with low-flow velocity, which was a stronger risk factor for WML than was high blood pressure. Perfusion MRI may become another alternative. A new modification of the Xenon-Spect method (Risberg, 2001) shows promising results with absolute values at high resolution and will significantly improve our knowledge on white-matter flow disturbances and mechanisms behind white-matter lesions.

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