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Journal of the Neurological Sciences 229–230 (2005) 3–6

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

The underdiagnosis of the vascular contribution to dementia

Amos D. Korczyn*

The Sieratzki Chair of Neurology, Tel-Aviv University Medical School, Ramat-Aviv 69978, Israel

Available online 8 January 2005

Abstract

The existence of vascular dementia (VaD) was first identified by Marie, who described the etat lacunaire, and by Binswanger, who identified white matter lesions in the brain subcortical areas. Alois Alzheimer, when defining the disease now bearing his name, did so in a patient with a presenile onset. The majority of demented elderly people were then believed to have cerebral arteriosclerosis underlying their cognitive decline. The role of cortical vascular lesions, while clear to clinicians, was highlighted only later, by the pathological studies of Tomlinson et al. and the clinical demonstrations of Hachinski et al. who have defined multi-infarct dementia. Lately, the emphasis shifted to pathogenic mechanisms for vascular brain disease with the identification of a multitude of processes, such as lipohyalinosis, cardiac dysfunction and genetic causes, to name only a few. Epidemiologic studies have demonstrated the high frequency of vascular lesions in brains of demented individuals, as well as the fact that vascular factors can contribute to Alzheimer's disease (AD). Moreover, many factors, which were identified as contributing to cerebrovascular disease in general and VaD in particular, are frequently suspected as predisposing to AD as well. All these considerations converge to the realization that vascular components are extremely important in the pathogenesis of old-age dementia and that prevention and perhaps treatment of dementia are within reach. These surprising findings highlight the importance of mixed vascular-degenerative dementia as a disorder that has to be properly defined.

Keywords: Vascular dementia; Diagnosis; Alzheimer's disease; Pathogenesis; Mixed dementia; Epidemiology; Prevention

Alzheimer's disease (AD) and vascular dementia (VaD) are considered the most common forms of dementia, and several attempts have been made to define each [1,4,11,19,20]. However, the clinical distinction between these two nosological entities may be difficult or even impossible. Because AD as well as atherosclerosis are age-dependent disorders, and because they are both so common, they inevitably occur together in many cases. Vascular lesions to the brain are frequently asymptomatic, presenting as "silent strokes", "asymptomatic lacunes" or white matter lesions. The onset of dementia is typically insidious in AD, and even when vascular damage underlies the cognitive decline, this does not necessarily take a "step-like" onset or course. In cases with vascular changes underlying an insidious cognitive decline, it is impossible to pin the onset date. Consequently, even if neuroimaging demonstrates evidence of stroke it is difficult to decide about the underlying pathology, which is thus frequently attributed to AD [15].

The slow evolution of AD is considered to result from accumulated loss of synapses or neurons. The classical view of VaD as being associated with step-like deteriorations may identify cases with multi-infarct dementia, but obviously does not cover the full picture. Clinically evident strokes typically cause identifiable motor or sensory deficits (and sometimes "cognitive" changes such as aphasia or apraxia); however, their association with insidious cognitive decline is more complex. In many cases, the cognitive changes are only identified, and possibly develop, slowly over weeks or months after the occurrence of a stroke [23]. However, another type of vascular cognitive syndrome, first described by Binswanger, is related to progressive white matter lesions that in many cases may be due to minute ischemic changes. Although Binswanger suggested that such white matter changes are sufficient, by themselves, to impair cognition, quite extensive white matter lesions can occur in cognitively

* Tel.: +972 3 6974229; fax: +972 3 6409113.
E-mail address: neuro13@post.tau.ac.il.

0022-510X/$ - see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.jns.2004.11.011

intact subjects, particularly in old age or on the background of hypertension or diabetes mellitus [8].

Demented individuals with white matter lesions frequently have associated brain changes such as hippocampal and cortical atrophy, either of which is a characteristic finding in AD [14]. However, atrophy of the medial temporal lobe is also very common in cases of VaD [2], and thus it might serve as a background on which the dementia develops after strokes. The common association of AD pathology and vascular changes has been repeatedly demonstrated in autopsy material [6]. Thus, the distinction between a primary neurodegenerative process such as AD and vascular brain damage cannot always be decided even by pathologists and no criteria for this differentiation are accepted. Moreover, there are several reasons to suspect that even pathologists cannot accurately diagnose VaD.

Firstly, the diagnosis of VaD can of course be made only if dementia exists. Obviously, the diagnosis of dementia of any kind is clinical, not pathological. In that respect, the pathologist depends on the clinical history of the patient. Neither AD pathology nor vascular lesions to the brain are necessarily accompanied by cognitive changes, and therefore all the pathologists can testify to is as to the existence of these types of damage, their location and severity.

Secondly, the designation of the dementia as being due to vascular lesions depends, inter alia, upon a temporal relationship between the two, e.g. ensuring at least that the cognitive decline only began after a cerebrovascular event. In that respect, the pathologist cannot usually add information as to the time of appearance of the vascular lesions, which might have occurred after the onset of cognitive decline, and thus cannot be held responsible for it [10]. Since pathologists typically examine the brain several years after the onset of the cognitive decline, they observe the cumulative burden of vascular damage and AD changes, which is likely to be larger than when cognitive decline started. Therefore, co-occurrence of vascular damage and cognitive decline at autopsy is probably higher than that which could be seen at onset of dementia. Furthermore, pathologists may not see the full picture and thus may underestimate the vascular changes. This is due to the fact that thorough examination of intracerebral blood vessels is not usually performed, myelin stains are not always done, and the brain is sliced at 5–10 mm intervals, thus possibly missing small lacunar infarcts [13]. Moreover, in many research-oriented laboratories only one hemisphere is cut, sparing the other for neurochemical studies, but leaving the pathologist ignorant about possible vascular lesions there. (Many of these problems could have been minimized if the autopsy would include a magnetic resonance imaging examination.) Therefore, at present, pathologists cannot be accepted as final arbitrators about the accuracy of diagnosis of VaD. A similar reasoning applies to pathological diagnosis of AD: the load of plaques and tangles is greater at autopsy than when the dementia began, while contributing vascular lesions may be missed.

The suggestion that many cases diagnosed as VaD are actually due to mixed (AD-vascular) etiology is supported by three lines of evidence.

Undoubtedly AD is a generalized brain disorder. In the cortex, widespread neuronal loss occurs accompanied (or preceded) by loss of synapses, leading to shrinking of the brain and sulcal widening. This general process, however, is primarily observed in the parietal and temporal lobes. The main histopathologic changes, depositions of amyloid and accumulation of neurofibrillary tangles, are similarly pronounced in these regions. While these changes define the hallmark of the pathological diagnosis of AD (the so-called Khachaturian criteria), they are by themselves insufficient. There is no biologically verified dividing line between the identical changes which are the inevitable consequences of aging, and any division is arbitrary. In fact, many elderly harbor these changes, sometimes extensive ones, without showing cognitive changes. While these ubiquitous changes are seen as pathognomonic for AD (and they are, by definition of the disorder), the fact that they can occur in non-demented elderly people poses an important question. If these changes are necessary but insufficient to cause dementia, what are the added pathological changes that are required. The answer, in many cases, is that vascular ischemic changes to the brain may tip the balance towards the development of cognitive decline. This was particularly demonstrated in the famous "Nun study" [21]. In this study, many elderly nuns who came to autopsy had the brain changes required for the pathological diagnosis of AD, but not all of those have been thought to be demented when clinically examined before death. The two subgroups, those with and those without dementia, did not differ significantly by the amount of deposited amyloid or neurofibrillary tangles, but rather by the co-occurrence of vascular lesions to their brains, sometimes quite discrete.

The central role of the hippocampus in memory processes had led to particular examination of changes to this structure in demented individuals. Indeed, medial temporal (or hippocampal) atrophy is constantly seen in AD. However, this change too is not specific to AD but seen very frequently in VaD cases [2].

A third cardinal manifestation of AD is the loss of neurons in the nucleus basalis of Meynert. These cholinergic cells in the basal forebrain are the origin of much of the cholinergic innervation of the cerebral cortex and their degeneration leads to cholinergic deficiency, which presumably contributes to the cognitive deficits in AD. This deficiency forms the basis of the therapy of AD with cholinesterase inhibitors. However, these changes too are apparently not specific to AD and can be seen very frequently in patients fulfilling diagnostic criteria for VaD. Changes in cell number, cortical choline-acetyl-transferase activity and other cholinergic markers have been amply documented [7,12,22,24].

These findings have led to attempts to treat VaD patients with cholinesterase inhibitors [17].