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MCI SERIES—IMPLICATIONS AND CONCLUSIONS

Vascular cognitive impairment: Evolution of the concept

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INTRODUCTION

Cerebrovascular and Alzheimer-type pathology coexist and interact. Most elderly patients have some degree of both, and vascular disease contributes to most cases of cognitive impairment and dementia (Cechetto, Hachinski, Whitehead, 2008; Schneider, Arvanitakis, Bang, & Bennett, 2007). Our understanding of the relationship between cerebrovascular disease and cognitive decline has evolved over the past 50 years (Libon, Price, Heilman, & Grossman, 2006; Merino & Hachinski, 2009).

Until the 1960s, most elderly patients with dementia were diagnosed with cerebral hypoperfusion due to atherosclerosis of the cerebral arteries. Over the next decade, however, several studies showed that episodic "large and small" strokes (and not chronic global hypoperfusion) were the cause of cognitive decline in patients with cerebrovascular disease (Fisher, 1968; Tomlinson, Blessed, & Roth, 1968, 1970); these findings led to the concept of multi-infarct dementia (MID) (Hachinski, Lassen, & Marshall, 1974). At the same time, as the result of scientific, societal, and political changes in the late 1960s and the 1970s, Alzheimer's disease (AD) was increasingly diagnosed and was considered the most common cause of dementia (Beach, 1987; Fox, 1989; Tomlinson et al., 1968, 1970). MID and AD were conceptualized as two distinct entities (Tomlinson et al., 1968, 1970). Hachinski developed the Ischemic Score to distinguish multi-infarct from degenerative dementia clinically (Hachinski et al., 1975).

In the next decade, several studies found that cerebrovascular lesions other than multiple infarcts also led to cognitive impairment and dementia, and the broader term vascular dementia (VaD) became popular (Loeb, 1985; Rivera & Meyer, 1975). Since the 1980s, several groups proposed different criteria for VaD (American Psychiatric Association, 1987, 1994; Chui, Victoroff, Margolin, Jagust, Shankle, & Katzman, 1992; Roman et al., 1993; World Health Organization, 1993). These criteria, however, have several shortcomings (Bowler & Hachinski, 1995). They identify patients in the later stages of the disease—the dementia phase—and paradoxically, while they exclude patients with neurodegenerative dementias, they are based on the Alzheimer's paradigm, with memory loss as the key clinical feature. Some include imaging criteria, but because of the requirement for a temporal relationship with stroke, they predominately identify patients with poststroke dementia. Furthermore, the criteria are not interchangeable, as they identify different patients (Amar, Wilcock, & Scott, 1996; Chui et al., 2000; Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2000; Wetterling, Kanaitz, & Borgis, 1996).

More recently, there has been an emphasis on detecting individuals with cognitive impairment in the brain-at-risk or the presymptomatic stage, when new lesions and further cognitive decline may be prevented (Hachinski, 1992, 2008). As detailed by Sachdev, Chen, Brodaty, Thompson, Altendorf, and Wen (2009) in this issue, for example, mild cognitive impairment in patients with stroke has negative prognostic implications; in their study, patients who were cognitively impaired 3 months after a stroke were more likely to progress to dementia than patients with intact cognition. In addition, there is growing awareness of the association of vascular risk factors, cerebrovascular disease, and AD (Cechetto et al., 2008; de la Torre, 2002; Viswanathan, Rocca, & Tzourio, 2009). The concept of vascular cognitive impairment (VCI) refers to a heterogeneous group of conditions in which vascular factors are associated with or cause cognitive deficits, and encompasses cognitive impairment of any severity caused by or associated with vascular factors, including patients without dementia and those with mixed vascular-neurodegenerative dementia (Bowler & Hachinski, 1995; Hachinski & Bowler, 1993; Moorhouse & Rockwood, 2008). It recognizes that vascular disease can interact with, potentiate the effects of, and even initiate neurodegenerative pathology, and that vascular dementia and AD are at two ends of a continuum, with most patients having a mixed etiology for cognitive decline (Viswanathan et al., 2009).

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AD and vascular pathology have a complementary and synergistic relationship, and there is a complex interaction between degenerative and vascular factors in the genesis of cognitive impairment (Knopman, 2006; Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001). Cerebral infarcts alter the clinical expression of a given load of AD pathology and increase the odds of having dementia among people with plaques and tangles (Snowdon, Greiner, Mortimer, Riley, Greiner, & Markesbery, 1997). Elderly patients often have coexisting Alzheimer and vascular pathology, and both processes may contribute to the development of cognitive impairment in most people with dementia (Schneider et al., 2007). AD and cerebrovascular disease have risk factors in common, including inflammation, diabetes mellitus, hypertension, atherosclerotic disease, and atrial fibrillation (Cechetto et al., 2008; Luchsinger & Mayeux, 2004). Vascular factors may play a role not only in the expression but also in the development of Alzheimer pathology. Microvascular damage is common in AD and changes in the vascular endothelium increase the cleavage of amyloid precursor protein, promote tau phosphorylation, inhibit clearance of amyloid, and may lead to the development of plaques (Stopa et al., 2008). Mechanistically, there are many similarities between the molecular pathologies of AD and stroke, including neuroinflammatory events and antioxidant depletion.

As highlighted in several of the papers in this issue, VCI is a complex nosological concept and because there are no pathognomonic features—no single pathological feature has a diagnostic value in an individual case—the diagnosis relies on clinical, radiological, and neuropsychological features. Delano-Wood, Bondi, Sacco, Jak, Libon, and Bozoki (2009) found, for example, that patients with mild cognitive impairment (MCI) can be differentiated into three distinct groups based on their cognitive profile, and that these profiles differ, presumably because of differences in etiology, by the extent and location of white matter changes seen on MRI. The association between risk factors, imaging findings, and cognition depends on the criteria used to define cognitive impairment. Jak and colleagues (2009) found that stroke risk and cognition were associated only if the diagnosis of MCI required impairment in two or more scores in a cognitive domain. They also found an association between MCI subtype and brain changes, because patients with amnestic MCI had smaller hippocampal volumes than patients with impairment in other cognitive domains. Zhou and Jia (2009) were able to differentiate MCI due to small vessel disease and early AD. Together the papers in this special issue show that understanding the contribution of vascular risk factors and cerebrovascular disease to the etiology of cognitive impairment is as important to a theory of mild cognitive impairment as it is for a theory of dementia.

Progress understanding the pathophysiology, clinical, and neuropsychological features of VCI and the development of new therapies is hampered by the lack of clear diagnostic criteria and an incomplete understanding of the interaction between vascular disease and neurodegenerative brain changes. Progress in the field is limited because of differences in study design. Comparison between studies in this issue, for example, is difficult, because they used different neuropsychological test batteries, definitions of cognitive impairment, and imaging criteria (Delano-Wood et al., 2009; Jak et al., 2009; Sachdev et al., 2009, Zhou & Jia, 2009). To address this methodological heterogeneity, and to foster research into VCI, the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) developed harmonization standards and defined a set of data elements that can be used in future studies to fully define VCI, understand its etiology, and identify targets for treatment (Hachinski et al., 2006). These standards are not meant to become dogma, rather they are open to debate, study, and validation. While developed to facilitate research, these harmonization standards can also be used to optimize clinical evaluation and care of patients with VCI. The NINDS-CSN harmonization criteria recommend the specific data points that should be sought and recorded in epidemiological studies and by clinicians caring for patients with potential VCI. They focus on several aspects of VCI that are important for diagnosis: clinical features, neuropsychology, neuroimaging, neuropathology, experimental models, genetics, biomarkers, and clinical trials. Rather than prescribe criteria, they provide screening questions to identify people with VCI, establish a minimum dataset for clinical practice or research studies, and develop an ideal dataset for VCI research. It is expected that their implementation will lead to data that, when integrated in a systematic manner, will be used to develop diagnostic criteria and evaluate new treatments.

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