Cerebral Ischemia and Alzheimer's Disease: Critical Role of PET and Implications for Therapeutic Intervention

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In 1907, Alois Alzheimer first described the neuropathological changes in the brain of a 51-yr-old woman with a progressive neurodegenerative illness that produced loss of intellectual and cognitive functions and eventually death (*1*). Initially considered to be a single entity, mounting evidence supports that Alzheimer's disease (AD) is an etiologically heterogeneous form of brain failure with common clinical and pathological features. These include progressive memory loss, behavioral changes, cognitive impairment, neocortical neurofibrillary tangles (NFTs), extracellular neuritic plaques and neuronal death. The pathological cascade(s) responsible for hyperphosphorylation of the microtubule-associated protein tau result in the formation of NFTs and the abnormal processing of the amyloid precursor protein, which eventually leads to the extracellular deposition of beta-amyloid and the formation of neuritic plaques have yet to be clearly delineated (*2,3*). Over the past 10 yr, genetic mutations have been identified on chromosomes 21, 14 and 31 that are capable of producing the clinical and pathological features of AD (*4–6*). In addition, the presence on chromosome 19 of the ε_4 allele for the apolipoprotein E gene is known to increase the risk for AD (*7*). This latter finding suggests that the presence of certain otherwise normal alleles may, when present in critical combination, effectively function as disease-modifying (or perhaps disease-causing) genes. Clearly, AD is etiologically and pathologically a complex neurodegenerative disorder, and no biochemical basis for this disorder has been established.

An analogous situation exists with regard to the potential contribution of comorbid conditions such as cerebrovascular ischemia to the clinical and pathological expression of AD. Although there is no evidence that cerebrovascular disease can produce NFTs or neuritic plaques, multiple infarctions or a single infarction in a critical area can cause dementia. What has remained difficult to determine is whether small-vessel ischemia, such as that often felt to be responsible for the subcortical high T2 signal intensity on MRI, contributes in a clinically meaningful way to the severity of the symptoms or rate of dementia progression in patients with probable AD.

In the U.S., approximately as many as 10% of individuals over age 65 suffer from some degree of dementia and the prevalence increases to approximately 40% by age 85 (*8*). The major causes of dementia in this group include AD (50%), multiple infarctions (5%) and a combination of AD and cerebrovascular disease (15%) (*9*).

The introduction of PET to determine regional cerebral blood flow and metabolism has improved substantially our understanding of the underlying pathophysiological mechanisms that are associated with many disorders of the brain, including cerebrovascular diseases (*10*). Using modern high-resolution instruments and appropriate positron-emitting tracers, local cerebral hemodynamic and metabolic function can be determined in detail. Current well-validated techniques allow noninvasive and quantitative measurement of cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMR O_2), oxygen extraction fraction (OEF), cerebral blood volume (CBV) and cerebral metabolic rate for glucose. Of great interest is determining the balance among these physiological and metabolic parameters in different phases of cerebrovascular disorders (*11*).

Several carefully designed studies have clearly demonstrated that after reduction in cerebral perfusion pressure, CBV increases as a result of dilation of arterial vessels (*12*). This in turn decreases vascular resistance and subsequently maintains CBF within normal limits. As maximal vascular dilation is achieved, further decline in perfusion pressure is followed by a proportionate decline in CBF. However, because of an increase in OEF in the affected brain tissue, CMR O_2 is maintained within normal ranges. It is well established that the OEF correlates with the ratio between CBF and CBV. Thus, CBF-to-CBV ratio represents a perfusion reserve, which may forecast the risk for future infarction. As perfusion pressure decreases further and all compensational mechanisms (vasodilatation and increased OEF) are exhausted, tissue infarction ensues. Ischemia (significant reduction in CBF and CMR O_2 without infarction) is considered a transient state and potentially can be reversed by initiating appropriate interventions. Therefore, detection of ischemia may have significant implications in the management of central nervous system (CNS) disorders, including those for which alterations in CBF are not considered the primary pathological process. AD, along with other neurodegenerative dementias, is only one example.

Research by Frackowiak et al. (*13*) demonstrated that both CBF and CMR O_2 were decreased in patients with AD and multi-infarct dementia (MID), and there was no evidence of increased OEF to indicate ongoing ischemia in either disease. This was a surprising finding because it was thought that ischemia may be a contributing factor to the clinical presentation of the disorder in patients with MID. Similar results were reported by Yao et al. (*14*), who also reported no evidence of ischemia in the involved white matter in patients with clinical and neuroradiological evidence of Binswanger's dementia.

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Nevertheless, significant cortical dysfunction was detected in the population examined. However, Meguro et al. (*15*), in a relatively larger sample of patients with periventricular hyperintensity and cerebrovascular risk factors, were able to demonstrate increased OEF and a decreased CBF-to-CBV ratio, which was pronounced in patients with severe lesions or in those who had evidence of Binswanger's dementia (*15*). The difference between the latter report and the results described by the other investigators can be attributed to some extent to the methodologies used and, in particular, to the resolution of the PET instruments used to conduct the investigation.

Histological examination of normally aging brain and patients with some CNS disorders has revealed various degrees of pathologic alterations in the white matter (*16*). However, the introduction of modern MRI techniques has provided unprecedented sensitivity for detecting white matter hyperintensity (WMH) in the otherwise normal brain and in various neurological diseases (*17*). Fazekas et al. (*18*) have characterized these lesions as punctate, early confluent and large confluent deep white matter abnormalities. Periventricular high signal intensity abnormalities were categorized as caps, smooth (halo) or irregular extending into deep white matter. A later work by Fazekas et al. (*19*) also revealed that in asymptomatic normally aging subjects, the presence and extent of white matter lesions correlated with the degree of cerebrovascular risk factors.

AD is a degenerative process that primarily affects the gray matter and associated cellular elements. Cerebral atrophy is secondary to neuronal degeneration and cell loss that is clearly detected on MRI. In contrast, MID predominantly affects the white matter, and adjacent and distant cortical dysfunction is caused by axonal deafferentation. In contrast to AD, which is considered a progressive and incurable disease, it may be possible to alter the course of dementias caused by cerebrovascular disorders by diet or medical or surgical interventions. Therefore, the coincidental diagnosis of ischemic abnormalities in patients with AD may provide a basis for therapeutic strategies. The incidence of such occurrences is not clearly established, but because the cerebrovascular risk factors are common among patients with AD, the possibility of this association should be explored because of its significant implications.

Yamaji et al. (*20*) attempted to provide further insight into the mechanisms responsible for WMHs in AD and the clinical consequences of such changes. Using PET and the ^{15}O-steady-state method, these investigators found CBF to be significantly lower in patients with WMHs whereas OEF was significantly increased. There was no significant difference in the pattern of these alterations nor in oxygen metabolism or CBV between patients with or without white matter signal intensity abnormalities. Based on these findings and a correlation of WMH severity with the mean OEF of cortical and white matter regions, the authors of this article conclude that these lesions are a consequence of latent ischemia. Preservation of oxygen metabolism suggests the absence of clinical correlates.

At first, these findings seem to fit well into current concepts of white matter damage in AD. As has been found in asymptomatic subjects, the frequency of signal hyperintensities in the deep and subcortical white matter of patients with AD is related to age and the presence of cerebrovascular risk factors (*19*). Histopathologic data support an ischemic cause of deep WMHs, and these lesions have been associated with only minimal neuropsychological consequences at a severity commonly found in AD (*21*). However, the WMH group of Yamaji et al. did not focus solely on AD patients who had more pronounced signal intensity abnormalities in the deep and subcortical white matter (*20*). Nine of their 16 patients were included because of a smooth band of periventricular hyperintensity. There is strong evidence for a nonischemic origin of this type of abnormality. Hyperintense periventricular bands have been observed more frequently in AD patients than in control subjects, even when correcting for possible effects of age and cerebrovascular risk factors (*22*). Histopathologic studies of brains in AD patients found no evidence for arteriolosclerosis in association with periventricular white matter changes (*23*). It should be also noted that a previous study of AD patients using SPECT and the ^{133}Xe inhalation technique found no correlation between CBF and periventricular hyperintensity. However, CBF of the central white matter and of the hippocampal region correlated significantly with the volume of deep WMHs (*24*).

The findings of Yamaji et al. (*20*) have demonstrated the potential of PET investigation by combining the assessment of CBF, CBV, OEF and oxygen metabolism for tackling complex pathophysiologic issues of subtle morphologic abnormalities. Also, they clarified that the contribution of WMHs to the severity of AD seems negligible. However, it is possible that these lesions affect the rate of cognitive decline, modify behavioral and other noncognitive symptoms and alter the response to antidementia drugs. Thus, future PET studies need to address the probable heterogeneity of WMHs. It also will be imperative to consider the effects of brain atrophy. PET studies of glucose metabolism in AD have demonstrated the crucial role of brain volume in the interpretation of functional data (*25*). Based on the reported association of periventricular hyperintensity with ventricular enlargement (*22*), the brains of the patients with WMH in the study of Yamaji et al. may have been significantly more atrophic, distorting CBF estimates to artificially low values. The finding of a somewhat reduced CBV in these patients instead of a compensatory increase would seem to support this assumption.

From a clinical perspective, the potential for effective therapeutic interventions to reduce cerebral ischemia raises the need for further studies. If white matter changes in patients with a coexisting neurodegenerative process such as AD adds to the burden of cognitive, behavioral or functional impairment, it would be reasonable to identify at-risk individuals and initiate appropriate diet or medication at the earliest possible point. Settling these issues will require careful studies in a well-characterized patient population with AD and the use of functional imaging tools such as high-resolution PET imaging techniques. It is only in this setting that we will be able to identify those patients who might benefit from specific pathologically targeted treatment strategies.

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