Topical Review

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Amyloid Burden, Neuroinflammation, and Links to Cognitive Decline After Ischemic Stroke

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One in 5 patients with stroke will end up demented shortly after a stroke, half with prior cognitive impairment and half without. After recurrent stroke, more than a third will become demented. The mechanisms remain unclear beyond the fact that neurodegenerative and vascular mechanisms contribute to the cognitive decline. In this review, we explore experimental and clinical evidence of interaction between ischemia, amyloid deposition, and neuroinflammation and identify new potential therapeutic targets.

Evidence From Experimental Studies

Clinical data clearly indicate that the coexistence of stroke and Alzheimer disease (AD) leads to exacerbated dementia, and experimental studies with animals have addressed the relationship between stroke and AD. Although human studies have also indicated that soluble parenchymal amyloid precursor protein and β-amyloid 1 to 42 (Aβ1-42) accumulate in patients with multi-infarct dementia, there are animal studies examining neurodegenerative mechanisms and cognitive impairment in global and focal experimental ischemia. Changes in neurotransmitter systems, trophic factors, and cell signaling and neuroinflammatory mechanisms have been well documented. Experimental animal models of cognitive impairment have demonstrated the presence of amyloid precursor protein in the area of ischemic damage. Studies in mice overexpressing mutated presenilin 1 or presenilin-knockout mice suggest that presenilin 1 mutations lead to enhanced neurodegeneration after focal ischemia or excitotoxicity. This may suggest that mutations leading to higher levels of Aβ may increase the sensitivity to ischemia. In another study, mice overexpressing amyloid precursor protein with middle cerebral artery occlusion were shown to have enlarged infarcts and a stronger reduction of blood flow after the arterial occlusion. These experiments, however, also showed that the vasodilatory effect of the endothelium-dependent vasodilator acetylcholine was significantly reduced in transgenic mice, possibly suggesting that Aβ-induced disturbance in endothelium-dependent vascular reactivity may contribute to the higher ischemia sensitivity. Our research group has conducted several studies directly examining the pathological, neuroinflammatory, and behavioral relationship of stroke and AD in rat and mouse models. In particular, these studies have focused on the potential synergism that would account for the clinical findings. A consequence of a chronic neuroinflammatory response is perturbation of the cerebrovascular system. Likewise, a perturbation of the cerebrovascular system will influence the degree of neuroinflammation after injury. A considerable body of evidence has demonstrated that AD is directly related to and has profound pathological changes in the cerebral microvasculature. Specific attention has recently focused on changes within brain endothelial cells in AD and in response to exposure to Aβ. It has been hypothesized that during the onset of AD the breakdown of the blood–brain barrier results in a neuroinflammatory response leading to increased transport of soluble Aβ across the endothelium, the upregulation of inflammatory adhesion molecule expression in response to nuclear factor xB, and subsequent infiltration of inflammatory leukocytes into the brain. This hypothesis has been supported by data showing that Aβ exposure of the basal compartment of endothelial monolayers in culture results in increased monocyte transendothelial migration. Interestingly, this migration of monocytes was inhibited by antibodies to the putative Aβ receptor for advanced glycation end products and to the endothelial cell–cell adhesion molecule platelet endothelial cell adhesion molecule-1, suggesting a significant role of Aβ in mediating inflammatory responses in AD. Despite overwhelming evidence for an involvement of dysfunction of the microvascular endothelium in the onset of AD, surprisingly little is known about the particular changes that occur in the endothelium in response to Aβ exposure and in response to various vascular risk factors in animal models that mimic the aspects of AD, stroke, diabetes mellitus, and hypertension. Given the strong links between neuroinflammation and the microvasculature, there is a strong rationale for examining the role of the microvasculature in rodent models of AD and stroke.
Neuroinflammation is a key component of the pathologies of both AD and stroke and involves proliferation of microglia and astrocytes, activation of the transcription factor nuclear factor κB, upregulation of inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, release of prostaglandin E2 under the enzymatic control of cyclooxygenase-2, and release of reactive oxygen and nitrogen species. Our previous work has demonstrated the following: (1) In a transgenic mouse model of AD (APP23 mice), small striatal infarcts induced with the vasoconstrictor endothelin-1 resulted in enhanced levels of inflammatory cytokines and AD-like pathology. (2) The combination of AD-like pathology induced by intracerebroventricular injections of the toxic 25 to 35 fragment of Aβ peptide (Aβ25–35) and stroke (unilateral endothelin-1 injections in the striatum) in the rat also resulted in enhanced neuroinflammatory responses and AD-like pathology in the neocortex and hippocampus and were correlated with memory deficits detected using the Barnes circular platform test. (3) Selective inhibition of the critical inflammatory transcription factor nuclear factor κB blocked the pathological and memory deficits associated with the rat AD model. (4) The neuroinflammatory, AD-like pathological changes and cognitive deficits in either the AD- or stroke-alone models were reduced with anti-inflammatory treatment, but not in the AD/stroke combined model. (5) This rat model of AD/stroke demonstrated progressive long-term deterioration of cognitive function. In parallel, there was a progressive increase in the size of the infarct and the neuroinflammatory response over time in the combined models of stroke and AD. Therefore, for stroke and AD, investigations indicate both conditions alone result in increased neuroinflammation that can be treated using anti-inflammatory agents. The combination of these 2 conditions elicited enhanced AD-like pathology, neuroinflammatory response, and memory deficits that are not ameliorated with anti-inflammatory treatment. This has led us to think that interactions between Aβ, stroke, and neuroinflammation may be occurring within the brains of some patients after a stroke, which may explain why they go on to develop dementia. Further work using innovative and sophisticated animal models needs to clearly demonstrate the timing between Aβ production, deposition, and the role of neuroinflammation after stroke and how this all related to the induction of cognitive decline. However, if this can be done, we can make the legitimate case for the concurrent use of anti-Aβ and anti-inflammatory therapies in human patients who suffered a stroke.

Evidence From Clinical and Epidemiological Studies

An association between ischemic stroke and poststroke cognitive decline or dementia has already been suggested in a subcohort of the Framingham Study and has been confirmed in prospective longitudinal studies. It was, however, not until the religious order study that an association between stroke, AD, or mild cognitive impairment and AD-specific pathology (parenchymal Aβ deposition) was described. Interestingly, subjects with subcortical infarcts had the highest risk of developing dementia and exhibited fewer AD pathologies than those without infarcts, whereas subjects with AD alone and subjects with AD with infarcts show otherwise similar clinical and risk factor characteristics. Whether ischemic infarcts only accelerate a pre-existing cognitive impairment or whether infarcts pose a risk for developing cognitive decline also in cognitively normal subjects remains unclear. Although 2 population-based cohort studies seem to support the view that prestroke cognitive status is an independent risk factor for poststroke dementia, other studies found no such association or only for nonannestic mild cognitive impairment but not for amnestic mild cognitive impairment, which usually is considered a prodromal state of AD. A recent longitudinal cohort study re-examining this question indicates that although higher levels of prestroke executive function are associated with lower risk for poststroke dementia (relative risk, 0.24; 95% confidence interval, 0.13–0.45), stroke was a disproportionate risk factor (relative risk, 4.4; 95% confidence interval, 1.35–14.63) for dementia in patients with high cognitive function. Based on these epidemiological studies and the results from animal experiments reviewed above, the following hypotheses explaining the relationship between stroke and AD pathology and poststroke cognitive decline have been put forward.

The Independence Hypothesis

This view is mainly based on epidemiological studies and assumes that multiple cortical or even small subcortical ischemic events as well as microvascular disease in general cause either direct cortical neuronal loss or subcortical damage, leading to a reduction of anatomic connectivity and to a sudden decrease in cognitive function from which patients may recover to some extent (trajectory A in Figure 1A). In case of additional presence of AD pathology (trajectory D in Figure 1A), these vascular ischemic processes decrease the reserve capacity of the brain to compensate ongoing neurodegeneration, thus preventing recovery of cognitive function. In this view, vascular processes are driving the poststroke cognitive impairment independently of the presence or absence of primary degenerative AD pathology.

The Interaction Hypothesis

The fact that patients with more severe cognitive impairment at the time of stroke are at high risk for developing dementia even in the absence of recurrent stroke might suggest that ischemic stroke triggers additional pathophysiological processes that may spark a secondary degenerative process (trajectory B in Figure 1A), which may interact with AD pathology and thus accelerate ongoing primary neurodegeneration (trajectory C in Figure 1A).

One such process could be hypoperfusion/hypoxia. It has been shown that in demented patients with unilateral internal carotid artery stenosis, Aβ deposits are significantly higher in the hemisphere with the stenosis, suggesting that chronic hypoperfusion (in the sense of a chronic penumbra) may indeed favor Aβ deposition. It remains, however, unclear whether such persistent hypoperfusion states are occurring frequently enough after acute strokes to explain the relatively high incidence of poststroke decline. A more promising
Pathophysiological process observed in conjunction with AD pathology as well as ischemic stroke is neuroinflammation and has thus been regarded as one possible link between the 2 pathologies. Recent progress in brain imaging methods, especially the combination of microglia imaging using positron emission tomography and diffusion tensor imaging using MRI, has demonstrated that persisting white matter inflammation after subcortical stroke can lead to the degeneration of fiber tracts over a 6-month observation period, which can even occur trans-synaptically in callosal fibers not directly affected by the infarct. Which factors are responsible for maintaining the inflammatory response over several months remains to be investigated with vascular risk factors (hypertension, dyslipidemia, or diabetes mellitus) or genetic factors being obvious candidates. It thus seems not unreasonable to assume that similar mechanisms affecting association fibers may lead to a decline in cognitive function (Figure 1B).

Imaging Aβ deposition in vivo using positron emission tomographic ligands is the third imaging component required to test these important hypothesis.

To demonstrate the feasibility of such a multimodal imaging study that could test these hypotheses, 7 patients with stroke were investigated to determine the spatial and temporal relationship between Aβ deposition, microglia activation, and cognitive performance. The 7 patients aged between 55 and 85 years with first supratentorial ischemic stroke underwent MRI scanning and the Montreal Cognitive Assessment (MoCA) <2 weeks and 5 to 7 months poststroke. Two positron emission tomographic scans were performed between 5 and 7 months after the event to assess Aβ deposition with Pittsburgh B compound (11C-PIB) and microglia activation with 11C-[R]-PK11195. Standardized uptake value ratios for 11C-PIB (SUVRPIB) in global gray and white matter relative to the cerebellum and uptake ratios for 11C-[R]-PK11195 (SUVRPK) between the stroke-affected and -unaffected hemisphere gray and white matter were analyzed.

The cognitive performance at 5 to 7 months after stroke (MoCA2) was negatively correlated with gray matter Aβ deposition (SUVRPIB; Figure 2). This relationship remained significant even when initial cognitive performance (MoCA1) and age were entered as covariates into the analysis. A multiple regression with MoCA1 and SUVRPIB as independent variables explained 98% of the variance in MoCA2 (adjusted $R^2=0.979; P<0.01$). Microglia activation in the stroke-affected hemisphere (SUVRPK) was mainly observed in white matter, Aβ deposits in the gray matter of both hemispheres (Figure 3). No significant relationship was found between gray matter SUVRPIB and SUVRPK.

The results of this hypothesis-generating pilot sample data in human stroke show that the imaging modalities and techniques to test the proposed hypothesis are available and that it may be possible to differentiate separate pathomechanisms.

Figure 1. A, Possible trajectories of poststroke cognitive decline. In the absence of parenchymal β-amyloid deposition, an ischemic infarct may cause a transient decline in cognitive function, but full or partial recovery is possible (trajectory A) without further deterioration of cognitive status. If vascular and inflammatory processes trigger ongoing secondary neurodegeneration, post-stroke cognitive decline occurs (trajectory B). In the presence of amyloid, the ischemic lesion causes a loss of cognitive reserve preventing cognitive recovery (trajectory D), and cognitive decline may even be accelerated if secondary degeneration is triggered by inflammatory processes (trajectory C). MoCA indicates Montreal Cognitive Assessment. B, Summary of hypothetical pathomechanisms leading to poststroke cognitive decline.

Figure 2. Linear regression between Montreal Cognitive Assessment (MoCA) between 5 and 7 mo poststroke (MoCA2) and cortical β-amyloid deposits measured with positron emission tomography and Pittsburgh B compound (11C-PIB; SUVRPIB). Regression analysis demonstrates a highly significant positive linear relationship between cognitive status poststroke and tracer uptake. This relationship remained significant after entering age and initial cognitive status (MoCA1, 2 weeks after stroke) into the analysis. SUVR indicates standardized uptake value ratio.
explaining Aβ-dependent cortical and non–Aβ-dependent but neuroinflammation-related subcortical mechanisms. A clinical trial investigating Determinants of Dementia after Stroke (DEDEMAS) with an Aβ imaging component is currently under way.51 True multicenter, multimodal imaging studies informed by the results from animal experiments, however, are still missing. Testing hypotheses such as those summarized in Figure 1B is clinically relevant because poststroke cognitive function is a major risk factor for poor long-term functional outcome after stroke, and the proposed imaging techniques might be useful to guide clinical interventions in preventing poststroke cognitive decline by modulation of inflammation or Aβ deposition.

In summary, neurodegenerative and vascular processes often occur together, but are usually studied apart. Poststroke cognitive impairment offers a good model of interaction, given that acute ischemia sets up a chain of rapidly evolving pathogenic events that can be studied, blocked, and modified experimentally as a guide to potential poststroke therapy.

**Disclosures**

None.

**References**


**Figure 3.** Examples for multimodal positron emission tomographic imaging in poststroke cognitive decline. Patient FDC (top) shows extensive t-amyloid (Aβ) depositions (left) but little to no microglia activation (right) together with a decrease in the Montreal Cognitive Assessment (MoCA1, 1 week; MoCA 2, 5–7 mo poststroke) scores. Patient BL exhibits persistent microglia activation 6 mo after the stroke but only little to no Aβ. She recovered cognitive function although not to normal levels.


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