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Understanding aging effects on brain ischemia

The authors of the papers in this special issue of Neurobiology of Disease address the highly relevant topic of the impact of aging on acute and chronic stroke. While aging is clearly an important factor impacting multiple aspects of stroke ranging from recovery to dementia, the mechanisms involved remain a mystery. This group of papers is a major step in filling that gap, which includes many causes, such as the use of young animals in stroke studies. Aging results in a new environment in the brain as some protective mechanisms available to young animals being lost and other detrimental aspects diminished. To improve stroke study design and to develop drugs, it is important to learn when these changes occur.

Aging dramatically changes blood vessels (Montagne, Pa et al. 2015). Diseases that increase with aging, such as hypertension, diabetes, and hyperlipidemia, are well-recognized risk factors that lead to changes in the blood vessels that promote stroke. Long-standing hypertension reduces the lumen of the blood vessels and increases fibrosis in the outer walls through changes in the extracellular matrix (Iadecola 2013). This causes fibrosis of a normally pliant blood vessel into a rigid vessel prone to inflammation. When the vessel lumen is reduced in size, a reduction in cerebral blood flow results that leads to hypoxia through hypoperfusion. The effect is to worsen outcome in the elderly brain in acute ischemia and to damage the deep white matter in chronic ischemia.

Part of the paradigm shift at NIH is a recent emphasis on understanding the role of white matter ischemia, which occurs in both acute and chronic ischemia, and several of the papers in this issue address that problem. Clearly, the vascular risk factors are a critical part of the pathobiology of white matter. The deep white matter is a region that is relatively oligemic. Hypoxia initiates a cascade of events that induces molecular mechanisms related to hypoxia that open the blood-brain barrier by inducing enzymes that attack the extracellular matrix (Rosenberg 2009). The disruption of the blood-brain barrier can be see directly by methods to measurer blood vessel permeability or indirectly by the recently developed diffusion tensor imaging (DTI) methods (Charlton, Schiavone et al. 2009). There is an increase in changes in the white matter that is normally present in the elderly and readily visualized with fluid-attenuated inversion recovery MRI (FLAIR). However, it is necessary to use DTI to determine whether the changes in the white matter represent an injury, making the findings on diffusion critical in diagnosis and treatment planning (Maillard, Carmichael et al. 2013).

While much research in stroke has focused on neuronal damage in the cortex, the injury to the white matter can cause major problems. The limited amount of white matter in the rodent brain has made it difficult to study. That is undergoing a change as evidenced by several papers on ischemia injury to white matter. The two main mechanisms are direct damage through strokes in the white matter, which result in disruption of the major white matter fiber tracts, impairing communication between the various brain regions and the slower injury produced under hypoxic conditions in the deep poorly perfused white matter. Improvements in diffusion MRI and in methods to measure functional connectivity with MRI have shown the devastating effects on cognition. This is a field of growing importance as the methods developed in animal studies are translated into humans, where the impact of disconnection of white matter fiber tracts can be readily studied with fMRI.

Aging has a major effect on cognition. The growing number of elderly, which is expected to swamp the medical systems in all countries has placed a special emphasis on dementia studies (Snyder, Corriveau et al. 2015). In the past several years these studies have undergone a major paradigm shift. After 30 years of research that has been based on the amyloid hypothesis, a series of high visibility therapeutic failures in treatment of Alzheimer's disease based on the removal of amyloid by antibodies and its reduction enzymatically, has reduced enthusiasm for a unitary approach to chronic brain diseases (Doody, Thomas et al. 2014, Salloway, Sperling et al. 2014). Autopsy studies reveal that not only are there amyloid plaques and neurofibrillary tangles in the aging brain of the patients with dementia, but that a high incidence of these patients show multiple pathologies with the most important one being ischemic injury (Toledo, Arnold et al. 2013). This finding of both Alzheimer's disease and vascular disease may be present in as many as 70% of patients, particularly as age increases.

Risk factors for stroke and chronic white matter damage are the typical ones involved in vascular disease in other organs (Gorelick, Scuteri et al. 2011). Understanding how these factors affect outcome in acute stroke and the damage in the white matter in chronic stroke is an area of active investigation. A number of papers in the special issue address this problem. The co-morbidities primarily increase injury to the white matter through a variety of mechanisms. They emphasize the importance of aggressively treating vascular risk factors, particularly in the younger patients since these changes are thought to begin around age 40 and extend into later years (Maillard, Seshadri et al. 2012). Longitudinal diffusion studies offer an excellent window into the progressive damage to the white matter.

The information contained in this group of reports provide insights into the molecular signals that can be used as biomarkers to detect the underlying pathobiology. Biomarkers will be the key to early detection of a pathological process in the brain. Some of these biomarkers reflect inflammation in blood vessels with release into the blood, allowing for detection. Others remain confined to the brain and require examination of the cerebrospinal fluid, which is invasive, making the blood biomarkers the most desirable, but the least informative. Alzheimer's disease research has advanced the biomarker field much further along than biomarkers for vascular disease. Since both diseases can be present, and both are affected by the co-morbidities discussed, understanding the interplay between the pathological changes related to

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multiple types of dementia will be an important area of future research.

Clearly the more we learn about the role of aging on ischemic damage both in the acute and chronic conditions will be critical in evaluating treatments and will provide an impetus for the important work in prevention that will occupy much of the research efforts in the years to come.

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