“Normal” and Pathological Changes with Age in the Brain

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Classical studies attempting to describe changes in the aging brain, such as cortical atrophy and reduction of neuronal number, may be inaccurate due to inclusion of brains with preclinical or early changes of neurodegenerative diseases such as Alzheimer’s disease (AD). AD pathologic changes, neuritic plaques and neurofibrillary tangles, are frequently seen in brains over 60 years of age, particularly in the most vulnerable areas, such as hippocampus and entorhinal cortex. If these changes represent preclinical AD, as opposed to the normal physiology of aging, then this will have a significant impact in the analysis and interpretation of earlier literature on aging.

There are macroscopic changes in the aging brain that are almost universally seen. Thickening of the arachnoid and prominence of the arachnoid granulations in the meninges are present. Increased ventricular volume is seen. Variable degrees of cortical and white matter atrophy have been reported. The degree of cortical (gray matter) atrophy must be interpreted with caution because of the potential inclusion of preclinical diseased brains in older studies, as mentioned above. Brain weight is reported to decline by several percentage points per year after the seventh decade; however, only minor gray-matter alterations have been noted if there is no cognitive decline in the patient. White matter lesions are very common in older brains, such as reduced volume and increased T2 signal on MRI, but their clinical significance is unclear. Vascular lesions are also common in aging brains, such as atherosclerosis and lacunar infarcts; however, these tend to be considered pathologic and not part of the spectrum of “normal” aging.

Discussion of age-related neuronal losses has been significantly improved with the advent of stereologic analysis. This involves a systematic random sampling of an anatomically-defined region of the brain using a counting scheme and mathematical rules to provide reliable and reproducible estimates of the total number of neurons in a given region, rather than relying on density-based measurements alone. Computer-based programs are ideal for performing this kind of analysis. Stereologic studies have shown that there is relative preservation of cortical neurons throughout the age spectrum, in stark contrast to classical studies, with perhaps a loss of only ten percent of cortical neurons over the entire lifespan. There may be subtle loss of neurons in specific regions of the hippocampus that are age-related. However, it is imperative to rule out an ischemic process, as the hippocampus is extremely vulnerable to ischemia, and animal models report no loss of hippocampal neurons with aging. Most subcortical structures also show neuronal preservation with age. The substantia nigra pars compacta is an exception; some degree of neuronal loss is seen with aging, approximately ten percent per decade.

The amount of neuronal lipofuscin pigment in large pyramidal cells increases with age. Lipofuscin consists of undigested carbohydrates, proteins, and lipids that are present in residual bodies derived from the lysosomal system. Certain neurons are particularly prone to lipofuscin accumulation, such as the cranial and spinal motor nuclei, red nucleus, lateral geniculate nucleus, globus pallidus, inferior olivary nuclei in the medulla, and dentate nucleus in the cerebellum. The significance of this accumulation is unclear. Accumulation may contribute to abnormal intracellular protein elimination. However, the nuclei most affected by lipofuscin accumulation are very little-affected by age-related neuronal losses.

Increased gliosis is present in aging brains. There is also a significant increase in the number of corpora amylacea (polyglucosan bodies) within astrocytic processes, particularly in the perivascular, subependymal, and subpial regions. They are also abundant at the base of the brain, olfactory tract, and spinal cord white matter. “Thorn-shaped” astrocytes that are positive for tau protein are seen in about 50% of brains by the eighth decade in the same distributions as the corpora amylacea. There is also microglial activation and granular degeneration of myelin in the white matter. The biologic significance of the white matter pathology is unclear.

Microscopic arterioles also develop changes with aging. Small venules in periventricular white matter show increased adventitial collagen deposition. Arteriosclerotic hyalinosis is present in the white matter, basal ganglia, and thalamus, which may be exacerbated by hypertension. Mineralization or ferrugination of vessels is frequently seen incidentally, particularly in the arterioles of the basal ganglia and capillaries of the molecular layer of the dentate gyrus in the hippocampus. Mild dilation of perivascular spaces, also known as cribriform change, is present in the white matter and basal ganglia.

Given that AD pathologic changes are frequently seen in older brains, one might ask if AD is an inevitable con-
sequence of aging. The answer is most likely no. AD usually begins with a failure of short-term memory. Memories are created via a physiologic phenomenon known as long-term potentiation (LTP) between hippocampal neurons. In animal models, LTP is harder to induce in aged rats, but reduction in synaptic strength (long-term depression) is easier to induce in these rats. LTP also decayed about twice as fast in older rats compared to young. Thus, faulty LTP mechanisms may be responsible for hippocampal neuron and synapse instability in aging. However, older animals do continue to learn and make new memories via LTP and do not exhibit symptoms of “dementia.” Moreover, reduced activity in the granule cells of the hippocampal dentate gyrus has been observed in old monkeys, but no abnormalities are appreciated in neurons in hippocampal areas CA1 and CA3. Area CA1 (Sommer’s sector) is the most severely affected part of the hippocampus in AD, but the dentate gyrus granule cells are unchanged in AD until very late in the illness. Thus, aging changes likely have different mechanisms than AD changes and are not necessarily interrelated. Aging is certainly a risk factor for developing neurodegenerative diseases such as AD, but AD is not necessarily an inevitable consequence of aging. In addition, pathologic criteria for diagnosing AD in the “oldest-old,” brains older than 90 years of age, break down. Patients with dementia in this age group have fewer neuritic plaques and neurofibrillary tangles in their brains, given their degree of dementia. This suggests that there are molecular and physiologic substrates of dementia that are masked by plaques and tangles in younger brains that need further elucidation in older brains.

References

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