Pathological aging of the brain

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The distinction between normal vs. pathologic brain aging is not as clear cut as one might think. The prevalence of various pathologic findings that are causally linked to dementia increases with age, for example neurofibrillary tangles, amyloid plaques, and cerebrovascular disease. What makes the notion of distinguishing pathological from normal brain aging difficult is the fact that the same pathologies that are causally linked to dementia are routinely found in subjects who were cognitively normal in life. At autopsy, virtually no cognitively normal 90 year old’s brain looks like a 20 year old brain. Recent longitudinal clinical studies with autopsy end points have focused attention on the idea that dementia in the elderly is most typically associated with multiple pathologies at autopsy. The most common pathological combinations leading to dementia in the elderly are Alzheimer's disease (AD) plus vascular disease, AD plus Lewy bodies, or all three.

Despite the above, the notion of specific dementing syndromes with distinct pathologic, clinical and imaging features is important for conceptualizing dementia. The four most common dementing disorders are discussed below: AD, vascular disease, Lewy body disease, and fronto-temporal lobar dementia.

AD is the most common cause of dementia in the elderly. It is characterized clinically by a progressive dementia which typically begins with isolated memory impairment. Declarative memory, (i.e., memory for explicit factual material) is the most profoundly affected cognitive domain early in the disease course. No absolute diagnostic test exists for AD. The diagnosis is based on clinical criteria and requires demonstration of a progressive deficit in more than one cognitive domain, usually memory plus another, after other possible causes of dementia have been excluded. The definitive diagnosis of AD can be made only on examination of tissue and therefore requires either autopsy, or biopsy. Two major risk factors for typical late onset AD are age and positive family history. Carriers of the apolipoprotein e4 allele are also at increased risk relative to non-carriers for typical late onset AD. The major pathologic features which characterize AD are senile plaques, neurofibrillary tangles, decreased synaptic density, neuron loss, and cerebral atrophy. MR findings associated with AD are as follows. Structural MRI demonstrates atrophy, which begins in medial temporal limbic areas and then spreads to association neocortex. ¹HMRS findings are decreased N-acetyl-aspartate and increased myo-Inositol. Choline findings have been less consistent with some studies reporting increase and others decrease in this metabolite. Diffusion imaging reveals increased apparent diffusion coefficients and decreased fractional anisotropy. Arterial spin labeling reveals decreased perfusion. Functional activation studies reveal decreased activation in more severely impaired subjects while increased activation has been reported in some studies in very mildly impaired subjects early in the course of the disease. Finally, resting state studies indicate decreased functional connectivity in the default mode network.
Cerebral vascular disease is regarded by some to be the second most common cause of dementia in the elderly after AD. While pure vascular dementia is considered to be relatively uncommon, vascular contributions to cognitive impairment are quite common. When considering the role of cerebral vascular disease in dementia it is therefore perhaps more appropriate to regard cerebral vascular disease as a type of brain pathology that is common in elderly subjects, and in combination with other pathologies, particularly AD, is a common contributor to cognitive impairment and dementia. It is helpful to establish some pertinent definitions. A stroke is a clinical event. Cerebral infarction is a pathological or imaging abnormality due to cerebral ischemia. Vascular cognitive impairment is cognitive impairment that can be attributed to brain injury due to cerebral ischemia. Vascular dementia is a subset of vascular cognitive impairment where cognitive impairment due to vascular brain injury results in significant functional impairment. Vascular dementia can occur without any obvious imaging abnormalities, but much more commonly with significant abnormalities on MR studies. Cerebro vascular lesions are commonly thought of in several categories: hemispheric infarction, subcortical (or lacunar) infarction, and white matter disease. Other types of cerebro vascular diseases associated with dementia are CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and amyloid angiopathy.

Dementia with Lewy bodies (DLB) is considered to be the second most common neurodegenerative cause of dementia in the elderly, accounting for up to 20% of dementia cases. DLB is slightly more common in men than women. The defining neuropathology of dementia with Lewy bodies is pathologic aggregation of alpha-synuclein protein in neurites to form Lewy bodies. Lewy bodies were first described by Frederick Lewy in a series of patients with Parkinsonism. Clinical diagnostic criteria for DLB have undergone several revisions, most recently in 2005. Features of the diagnostic criteria are ranked as central, core, suggestive, and supportive. The central feature which is essential for a diagnosis is dementia. Core features are fluctuating cognition, recurrent visual hallucinations, and spontaneous Parkinsonism. Suggestive features are rapid eye movement (REM) sleep behavior disorder, severe neuroleptic sensitivity, or functional imaging showing low dopamine transporter activity in the basal ganglia. Imaging features associated with DLB have largely been associated with nuclear medicine techniques. These include occipital hypoperfusion with functional imaging; decreased dopamine transporter activity in the basal ganglia with SPECT or PET radioligands; decreased uptake of metaiodobenzylguanidine on cardiac syntography. MRI findings have largely been exclusionary. However, recently a pattern of focal atrophy confined to the dorsal pontomesencephalic junction, peri third ventricular gray matter, and substantia innominata was identified on voxel-based morphometry.

Frontotemporal lobar dementia (FTLD) describes a family of neurodegenerative disorders characterized by focal lobar degeneration of the frontal and/or temporal lobes. The umbrella term frontotemporal lobe
degeneration is commonly divided into three clinical syndromes or subtypes. These are frontotemporal dementia, semantic dementia, and non-fluent aphasia. While AD and DLB account for the majority of neurodegenerative dementias in individuals greater than age 65, FTLD is as common as AD in subjects under the age of 60. Imaging findings on structural MRI closely mirror the observed clinical syndromes in FTLD. Patients presenting with the behavioral FTD variant tend to show bilaterally symmetric frontal or predominantly right frontal atrophy. Patients presenting with semantic dementia tend to show predominantly anterior temporal atrophy with left sided predominance if speech apraxia predominates and right sided dominance if prosopagnosia predominates. Patients presenting with nonfluent aphasia tend to have atrophy involving the left frontal and insular areas.