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REVIEW

Clinical Anatomy of the Most Common Dementias

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INTRODUCTION

According to Van de Flier et al. (2005), dementia is a progressive deterioration of cognition that can be caused by several underlying factors affecting particular areas of the brain to generate specific clinical features. Certain diseases cause dysfunction in the cerebral hemispheres, subcortical nuclei or white matter interconnections, leading to dementia (Schafer et al., 2016). In this review, the focus will be on the clinical anatomy of the major types of dementia in order of prevalence, Alzheimer's disease being the most prevalent, followed by vascular dementia, frontotemporal dementia and dementia with Lewy bodies.

ALZHEIMER'S DISEASE

According to Bakkour et al. (2013), Alzheimer's dementia is diagnosed clinically when a patient loses memory, executive function, language, visuospatial function and other abilities owing to pathological changes in multiple areas of the cerebral cortex and other parts of the brain. A diagnosis of Alzheimer's disease is confirmed essentially by the pathological discovery of extracellular neuritic/$\alpha\beta$-amyloid plaques and intracellular neurofibrillary tangles in postmortem autopsies (Hyman et al., 2012). Dickerson et al. (2009) described Alzheimer-affected brains as showing marked cerebral atrophy especially in the inferior temporal gyrus, medial temporal lobe, posterior cingulate/precuneus and inferior parietal lobule, where the sulci widen and the gyri thin. These are typically the earliest areas to start thinning even in the mildest Alzheimer's cases. Other cortical regions, particularly the superior parietal and frontal cortex, show no appreciable thinning until Alzheimer's symptoms are more prominent. Other researchers have also found pathological hallmarks of Alzheimer's in other areas of the brain such as the hippocampus, along with the surroundings of the hippocampus comprising the perirhinal, parahippocampal, and entorhinal neocortical regions (Detoledo et al., 1997; Jack et al., 1998). These areas that are markedly affected in Alzheimer's are spared or negligibly atrophied during normal aging. As a result, episodic memory, semantic memory, and executive and visuospatial-attentional networks are disrupted early in the clinical phase of Alzheimer's disease (Bakkour et al., 2013). Researchers have also revealed a loss of neurons in subcortical areas such as the basal nucleus of Meynert (Arendt et al., 1983), locus coeruleus (Hoogendijk et al.,1995), nucleus raphe dorsalis (Aletrino et al., 1992), and pedunculopontine nucleus (Jellinger et al., 1988), contributing to the progression of Alzheimer's disease. The defects are visible as paler-colored substantia nigra and locus coeruleus areas. The loss of neurons creates symmetrically dilated ventricles called hydrocephalus *ex vacuo*.

Neurofibrillary tangles are clinically correlated with the severity of Alzheimer's symptoms (Goedert et al., 1993). German et al. (1997) described the tangles as being seen first in the hippocampus, parahippocampal areas and enterohinal cortex, where much younger patients are asymptomatic. Alzheimer's disease progresses because of the accumulation of NFTs in the temporal cortex, causing mild cognitive impairment (MCI), and becomes full blown when NFTs appear in the neocortex, deep nuclei that project to the cortex such as the locus ceoruleus, dorsal raphe nucleus, paranigral nucleus and midline thalamic nuclei along (diffusely) with the brainstem (Arnold et al., 1991).

Neuritic plaques, on the other hand, cover an extensive part of the cerebral cortex gray matter at the end stage of Alzheimer's disease (Dickson, 1997). These plaques do not correlate with the clinical severity of Alzheimer's as NFTs do (Jack et al., 2010).

Perrin et al. (2009) showed that cortical and hippocampal volume loss is hard to quantify precisely during early stages of Alzheimer's and also at

Abbreviations: CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DAT, dopamine transporter; FDG-PET, fluoro-deoxyglucose-positron emission tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging

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postmortem, but not difficult with high resolution quantitative magnetic resonance imaging (MRI), which is especially useful in distinguishing between the neurodegeneration of normal aging and early Alzheimer's. Using ventricular expansion and regional loss of volume, it also predicts disease progression from normal cognition to MCI to Alzheimer's. The downside is that it cannot reveal the pathology underlying the neurodegenerative process. As neurons in the medial temporal lobe and hippocampus are susceptible to neuronal loss especially in early Alzheimer's, functional MRI studies are helpful in revealing synaptic activity in these areas. During MCI, these areas show hyperactivation owing to neuronal compensation for functional inefficiency. In the clinical stages of Alzheimer's, these same structures are hypoactive. Other methods described by Perrin are: Single photon emission computed tomography, which measures regional blood flow; Pittsburgh Compound-B-Positron Emission Tomography, which binds and quantifies amyloid; and Fluoro-Deoxyglucose-Positron Emission Tomography (FDG-PET), which measures glucose metabolism (reduced in Alzheimer's). These techniques, along with functional MRI, can predict the progression from MCI to Alzheimer's disease.

VASCULAR DEMENTIA

It has been proposed that vascular dementia is caused by multiple infarcts, but other factors have been shown to contribute to it in addition to their association with Alzheimer's (Tomlinson et al., 1970; Hachinski et al., 1974). Vascular dementia can now be classified under the umbrella term vascular cognitive impairment, a multifactorial set of conditions: different causes can contribute to the spectrum of vascular diseases that lead to cognitive impairment and dementia. Because the pathology of vascular dementia is diverse, the clinical signs and symptoms are also diverse. They depend on the type, number, location, volume and severity of stroke. Ischemic strokes lead to more morbidity than hemorrhagic strokes because the survival rate is higher (Kalaria et al., 2016).

Three main subtypes of pathological entities contribute to vascular cognitive impairment, as discussed in detail below: large vessel stroke, small vessel stroke and mixed pathology.

Large vessel strokes include strategic infarcts, multi-infarct dementia and post stroke dementia. Staekenborg et al. (2008) described the clinical features of large vessel strokes as defects specific to certain areas that are also associated with higher risks for hemimotor dysfunction, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry, and hemiplegic gait disorder.

Strategic infarcts cause dementia when cortical or subcortical areas are targeted, resulting in cognitive impairment. Affected locations in the cortex include the medial frontal lobe, inferomedial area of the temporal lobe, angular gyrus and hippocampus. When the hippocampal memory loop (of Papez) is injured, this causes dementia. Bilateral obstruction of the posterior cerebral artery produces amnesia and visual field defects because blood flow to the posterior medial hippocampus is compromised (Benson et al., 1988). Subcortical lesions in, e.g.. the fornix, caudate nucleus, anterior limb of the internal capsule, globus pallidus or thalamus can also produce amnesia. Lesions in the basal forebrain and thalamus involving pathways to the amygdala and hippocampus can cause severe amnesia; in contrast, when only one pathway is affected, only MCI results (Cipolotti et al., 2008). Rupture of an aneurysm in the basal forebrain can cause significant amnesia with personality changes (Damasio et al., 1985).

It is traditionally believed that multi-infarct dementia is common; multiple cortical infarcts cause a stepwise development of dementia, but it is very uncommon for a single entity to cause it (Kalaria et al., 2016). According to Jin et al. (2008), post-stroke dementia develops within a year after stroke in two thirds of patients, usually of advanced age, with pre-existing pathologies such as vascular and/or degenerative changes in the brain, e.g., Alzheimer's disease, multiple infarcts, strategic infarcts or subcortical ischemic dementia.

Subcortical small vessel dementia is a syndrome revealed by cognitive, clinical neuroimaging, and neuropathological findings. It is thought to arise from disease affecting the perforating cerebral arterioles, capillaries, and venules, resulting in injuries to the cerebral white and deep grey matter (Pantoni, 2010). It has a subacute onset, the main forms being lacunar stroke, white matter hyperintensity, Binswanger disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral amyloid angiopathy and microinfarcts. Dysarthria, dysphagia, Parkinsonian type gait disorder, and hypokinesia are more prevalent in patients with small vessel disease (Staekenborg et al., 2008).

Lacunar infarctions, according to Donnan (1993), are rounded, ovoid, or tubular infarcts usually $<$20 mm in axial diameter and are most common in the basal ganglia or internal capsule. Areas such as the thalamus and putamen have been implicated in more severe dementia than areas in the caudate, capsule and white matter (Benisty et al., 2009). Bilateral thalamic lesions are associated with increased risks for dysphagia, Parkinsonian type gait disorder, and hypokinesia (Staekenborg et al., 2008). Acute lacunar infarcts shrink and can leave small cavities (lacunes) or even larger stiratocapsular lesions that have signals similar to white matter hyperintensities. The presence of multiple lacunes is also associated with an increased risk of hemimotor dysfunction (Staekenborg et al., 2008). White matter hyperintensities or leukoaraiosis are periventricular or located in white matter distributions in the cerebral cortex, basal ganglia, pons, other parts of the brain stem and cerebellar white matter. They have been shown to reduce cognitive and lower extremity functions, the most important of many risk factors being hypertension, as shown in different studies (Jeerakathil et al., 2004; Pantoni et al., 2010; Maillard et al., 2012). Extensive leukoaraiosis is associated with increased risks for dysarthria, dysphagia, Parkinsonian type gait disorder, and rigidity (Staekenborg et al., 2008).

Lacunar strokes and leukoaraiosis overlap in terms of pathology but contribute independently to the development of dementia (Van Der Flier et al., 2005). On imaging, they are rounded areas of decreased attenuation on CT scan, increased signaling on T2 and FLAIR MRI. Binswanger disease is an ischemic periventricular leukoencephalopathy due to chronic hypoperfusion and critical stenosis of the medullary arterioles, causing widespread incomplete infarction of the white matter that typically spares the short commissural U-fibers (Donkelaar et al., 2011). CADASIL is a rare autosomal dominant arteriopathic cause of dementia, severe white matter disease and headaches (Schafer et al., 2016). It is characterized by subcortical white matter lesions affecting the poles of the temporal lobes along with the brain stem, particularly in the pons (Chabriat et al., 1998).

Cerebral amyloid angiopathy is an accumulation of β-amyloid peptide in medium-sized to small arteries in the superficial cortex and leptomeninges, causing cerebral hemorrhages that lead to dementia if there are enough of them at critical locations. Vascular dementia associated with Alzheimer's pathology is proven to have worse outcome than Alzheimer's alone (Pfeifer et al., 2002). Microinfarcts especially in the deep hemispheric and infratentorial regions as revealed on autopsy have been shown to be as detrimental as macroinfarcts and increased Alzheimer-related pathology in terms of brain atrophy (Longstreth et al., 2009).

Mixed vascular dementia and Alzheimer's disease is important because most patients with dementia at autopsy had multiple pathologies, most commonly (up to 38%) this subtype of vascular dementia, as seen in the study by Schneider et al. (2007). Alzheimer's disease is associated with a considerable amount of cerebrovascular pathology, such as small vessel disease and microinfarctions including vascular amyloid angiopathy, which can cause cognitive impairment independently of plaques and tangles (Kalaria et al., 2016). When vascular disease and Alzheimer's disease coexist, less Alzheimer pathology is needed to cause dementia (Nagy et al., 1997). Snowdon et al. (1997) conducted a Nun Study in which the more demented patients had 20 times more Alzheimer pathology and lacunar strokes, as revealed at autopsy.

The imaging lesions of vascular dementia include those types causing small-vessel disease, usually affecting at least 25% of the white matter along with multiple basal ganglia and frontal white matter lacunes, and bilateral thalamic lesions (Guermazi et al., 2007). Conventional MRI can show lacunar infarcts or hemorrhages, lacunes, white matter hyperintensities, perivascular spaces, microbleeds and atrophy in affected patients. Advanced MRI techniques such as diffusion tensor imaging, spectroscopy, and functional methods can show microinfarcts, disrupted axonal connections, altered white matter integrity, increased brain water content, altered myelination and secondary focal thinning of the cortical grey matter (Wardlaw et al., 2013). Other techniques used are FDG-PET for measuring regional cerebral glucose metabolism, which shows decreased uptake in areas most affected by microvascular white matter disease, especially the frontal lobes and deep nuclei. Cerebral blood flow can be measured using single photon emission computerized tomography (SPECT) or arterial spin label (ASL) imaging (Roman et al., 2012).

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia, also known as Pick's disease, is a rare form of progressive dementia in which the right prefrontal and anterior temporal cortices are predominantly atrophic, causing changes in behavior as part of the spectrum of frontotemporal lobar degeneration or FTLD (Trojanowski et al., 2001). This is also called behavioral variant FTLD; the anatomical regions typically affected are the dorsolateral cortex, medial frontal cortex, orbitofrontal cortex, amygdala, insula and anterior cingulate cortex. There are also associated atrophic changes in the basal ganglia and depigmentation of the substantia nigra. The atrophy can become so severe that gyri and white matter are narrowed to slivers, called knife-edge atrophy. This causes an early decline in personal and social inhibition, dysfunction in executive functioning and loss of insight (Wang et al., 2007). Other forms of FTLD can be determined by the location of the lobar degeneration: left inferior frontal atrophy causes progressive non-fluent aphasia while predominantly left anterior temporal atrophy causes semantic dementia. Non-fluent progressive aphasia patients show significant left cortical atrophy in the inferior and middle frontal, precentral, anterior insula and caudate regions with such symptoms as non-fluent spontaneous speech, phonemic paraphasias, agrammatism and anomia (Gorno-Tempini et al., 2004 and Kertesz et al., 2005). On the other hand, Mummery et al. (2000) described semantic dementia as associated with behavioral and emotional disturbances, like behavioral variant FTLD, but differing qualitatively in respect of depression, loss of empathy and emotional blunting. These changes are due to the degeneration of the orbitofrontal and right anterior temporal lobe and of the amygdala. The left hemisphere is also involved, but at the middle and inferior temporal gyri and ventromedial frontal lobe. Patients also develop prosopagnosia and loss of visual object meaning when the right hemisphere is more involved than the left (Snowden et al., 2001).

DEMENTIA WITH LEWY BODIES

According to McKeith et al. (2005), dementia with Lewy bodies is a neurodegenerative dementia characterized by deficits in attention, executive functioning and visuospatial perception, with better preservation of memory and naming skills than in Alzheimer's. There is also autonomic, sleep, neuropsychiatric and motoric dysfunction. Dementia with Lewy bodies is a synucleinopathy hallmarked by Lewy bodies, mainly affecting the cerebral cortex and brain stem (O'Brien, 2006). Lewy bodies are also described in Parkinson's disease, accumulating in the hypothalamus, nucleus basalis of Meynert, sympathetic, substantia nigra, dorsal vagal nucleus and locus coeruleus. Parkinson's disease patients often develop a dementia that is

clinically different from dementia with Lewy bodies in that it usually develops after the symptoms of Parkinsonism, but there is not much difference anatomically except for more neuronal loss in the substantia nigra contributing to the Parkinsonian symptoms (Tsuboi, 2005).

Areas predominantly affected in the cortex in dementia with Lewy bodies are the frontal (especially the cingulate gyrus), insular, temporal and parietal areas (Duda et al., 2002). Yachnis et al. (2014) described Lewy neurites as most common in the hippocampus, parahippocampal gyrus and amygdala. Donkelaar et al. (2011) explained that there are no macroscopic abnormalities characteristic of or specific for dementia with Lewy bodies. Hypopigmentation of the substantia nigra and locus coeruleus was observed as along with mild diffuse frontotemporal and hippocampal atrophy. There are increased Lewy bodies in the amygdala and anterior and inferior temporal lobes at autopsy associated with visual hallucinations (Harding, 2002). Lewy bodies are also seen in the intermediolateral cell column of the spinal cord, hypothalamus, and dorsal vagal nuclei, which correlates with the dysautonomia seen in dementia with Lewy bodies (Benarroch et al., 2006). Benarroch et al. (2009) also conducted a pathological study and found far fewer dopaminergic neurons in the periaqueductal gray area in the midbrains of affected patients than in controls, and this was correlated with excessive daytime sleepiness.

Both Parkinson's disease dementia and dementia with Lewy bodies have more cortical Lewy body density than Parkinson's disease, especially in the limbic system, and this contributes to the cognitive dysfunction seen in both dementias. Braak et al. (2003) suggested that the initial pathology of Parkinson's disease and Parkinson's disease dementia is in the lower brainstem nuclei, spreading subsequently to the substantia nigra, then to the basal forebrain and finally the cortex. Tsuboi et al. (2005) suggests that the initial pathology for dementia with Lewy bodies is in the limbic system and basal forebrain.

Clinical diagnosis of dementia with Lewy bodies includes the use of functional imaging of the dopamine transporter (DAT), which differentiates it from other causes of dementia such as Alzheimer's by measuring nigrostriatal dopaminergic uptake (especially in the putamen), which is significantly lower than in Alzheimer's, where uptake is normal (Dubois et al., 2007). Other imaging studies used include structural MRIs, which show putamen and posterior mesopontine atrophy with preserved hippocampal and medial temporal lobe volumes (Whitwell, 2007). On a SPECT scan, occipital hypoperfusion (Lobotesis et al., 2001) is seen, while on FDG-PET there is occipital hypometabolism (Minoshima et al., 2001) without corresponding occipital atrophy on structural MRI. FDG-PET also shows relative preservation of posterior cingulate metabolism relative to precuneus and cuneus metabolism, and this is is the most specific way to distinguish dementia with Lewy bodies from Alzheimer's (Graff-Radford et al., 2014). Amyloid imaging is also used; dementia with Lewy bodies patients are positive for amyloid but have less deposition than Alzheimer's patients (Edison et al., 2008).

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