The neuropathology of neurodegenerative diseases causing dementia

William W Pendlebury

Abstract

The dementia syndrome is increasing in prevalence throughout the developed world as the population ages. For example, in the United States it is estimated that between 2000 and 2020, the number of people living to 100 years or more will increase by over 200%, and the number of people surviving to 90–95 years will double. Based on these and other epidemiologic data, the prevalence of diseases causing the dementia syndrome has and will continue to increase dramatically over the next several decades. Considering Alzheimer's disease alone, the most common cause of dementia in the elderly, there are currently 5.5 million persons affected in the United States, and that prevalence will increase to 16 million by the first half of this century. This review will focus on the histopathology of important neurodegenerative diseases of the brain that cause dementia, including Alzheimer's disease, frontotemporal lobar degenerations, and dementia with Lewy bodies. In addition, a less common but extraordinarily interesting condition, chronic traumatic encephalopathy, will be reviewed.

Keywords Alzheimer's disease; chronic traumatic encephalopathy; dementia; dementia with Lewy bodies; frontotemporal dementia; frontotemporal lobar degeneration

Introduction

Starting at the age of 60 years, at which time the prevalence of dementia is about 1%, the prevalence doubles for each 5 year epoch. As such, the estimated prevalence of dementia for people over age 85 years approximates 32%. Some epidemiologic studies suggest that the prevalence may be as high as 50% in this age group, and in the United States the cohort of individuals over the age of 85 years is the fastest growing subset of the population.[1] Based on this epidemiologic data, incident cases and the prevalence of dementia will continue to increase over the next several decades. In the United States, Alzheimer's disease represents the fifth leading cause of death in people over the age of 65 years, and the sixth leading cause of death overall. Healthcare cost related to Alzheimer's disease worldwide is estimated to be 600 billion dollars annually and, in 2014, United States healthcare cost was over 214 billion dollars, making Alzheimer's the third most expensive disease after heart disease and cancer.

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Autopsy examination of the brain remains the gold standard for the pathologic diagnosis of neurodegenerative diseases causing dementia. Brain biopsy is no longer considered necessary or practical in the vast majority of dementia cases, although may be performed uncommonly in instances of an atypical clinical phenotype or unusual progression of disease. Gross examination of the brain reveals no specific or unique characteristics for any of the neurodegenerative diseases considered in this review. For example, the brain of a patient with clinical Alzheimer's disease does not show any grossly apparent alteration that can be considered to be diagnostic, and there is considerable overlap with brains from elderly patients who were cognitively normal prior to death.[2] Characteristic features that may be seen in an Alzheimer's disease brain include generalized atrophy that spares the primary motor, sensory and visual cortex; symmetrical ventriculomegaly; thinning of the corpus callosum and anterior commissure; and especially hippocampal atrophy associated with dilated temporal horns of the lateral ventricles. Again, it should be noted that any of these features may be seen in the brain of a cognitively normal individual, and the brain of some patients with Alzheimer's disease may show no grossly visible abnormalities.

In a similar fashion, gross brain examination of a patient with one of the frontotemporal lobar degenerations may or may not show characteristic features. As an example, the brain of a patient thought to have behavioral variant frontotemporal dementia (historically Pick's disease) may show selective atrophy of the frontal and anterior temporal lobes, or may appear grossly normal. This review will focus on microscopic changes found in selective neurodegenerative diseases causing dementia, and will include some discussion of diagnostic criteria and pathogenesis.

Alzheimer's disease

Since the original description by Alois Alzheimer of the disease that bears his name,[3] much has been learned about the nature and distribution of microscopic lesions in the brain of affected individuals. One can consider the microscopic findings to be both positive and negative, with the classic positive lesions including amyloid plaques and neurofibrillary tangles (Figure 1), Hirano bodies, and granulovacuolar degeneration of Simchowitz. Negative findings include neuronal and synapse loss that several studies[4] have found to be the best correlates of cognitive decline, particularly in the neocortex and limbic systems. An additional, almost constant, finding is that of cerebral amyloid angiopathy, a vasculopathy affecting principally capillaries, small arterioles, and medium sized arteries of the leptomeninges and superficial neocortex. Cerebral amyloid angiopathy will be described in greater detail below.

Neurofibrillary tangles: Neurofibrillary tangles (NFTs) (Figure 2) were first described by Alois Alzheimer in his original autopsy case report as intraneuronal filamentous inclusions within the parikaryal region of pyramidal neurons. Ultrastructural studies have shown that NFTs are composed of paired helical filaments (PHFs) that are fibrils of 10 nm in diameter that form pairs with a helical conformation at a regular periodicity of about 65 nm.[5] The major constituent of NFTs is that of a microtubule associated protein called tau (Figure 2a), one of a

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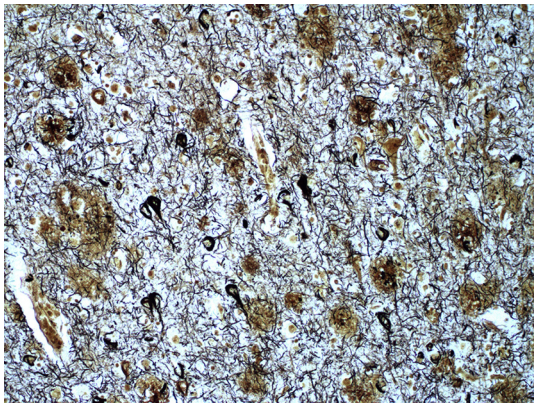

Figure 1 Bielschowsky silver impregnation stain showing the classic lesions of Alzheimer's disease, amyloid plaques and neurofibrillary tangles.

family of proteins that function to stabilize the microtubule assembly. For reasons that are not entirely understood, in Alzheimer's disease tau disassociates from microtubules, becomes hyperphosphorylated, and self assembles into PHFs. Although NFT's can be visualized on a hematoxylin and eosin stained section of hippocampus (but not neocortex) (Figure 2b), a silver impregnation stain such as the Bielschowsky technique is the preferred method for detecting NFTs. Mature NFTs consist of cytoplasmic filamentous aggregates of tau that displace the nucleus toward the periphery of the soma (Figure 2c). NFTs are most characteristically found in the cornu ammonis 1 (CA 1) sector of the hippocampus and layer V neurons in areas of the association neocortex. Severe involvement of NFTs is seen in the layer II neurons of the entorhinal cortex, the CA 1 and subicular regions of the hippocampus, the amygdala, and the deeper layers of the neocortex.[6] Studies have shown that the extent and distribution of NFTs in cases of Alzheimer's disease correlate with both the degree of dementia and the duration of illness. From that prospective, Braak and Braak[7] distinguished six stages of development and distribution of NFTs that correlate with the development of clinical dementia. The first NFTs consistently appear in the entorhinal region (stage I), followed by the CA 1 region of the hippocampus (stage II). Next, NFTs develop and accumulate in limbic structures such as the subiculum of the hippocampus (stage III), and the amygdala and thalamus (stage IV). Finally, NFTs spread to all neocortical areas, first involving the association areas (stage V), followed by primary motor, sensory and visual areas (stage VI).

Amyloid plaques: The amyloid plaques (Figure 3) described by Alois Alzheimer in his original case report[3] result from the abnormal extracellular accumulation and deposition of the amyloid-β peptide (Aβ) with 40 or 42 amino acids (Aβ40 and Aβ42). These represent two normal byproducts of the metabolism of the amyloid precursor protein, a transmembrane neuronal protein, after its sequential cleavage by the enzymes β- and γ-secretases. Because of the higher rate of fibillization and insolubility, Aβ42 is more abundant than Aβ40 within the plaque. Why people with Alzheimer's disease accumulate Aβ42 and Aβ40 is unclear; hypotheses include overproduction in or decreased clearance from the brain. As with NFTs, amyloid plaques can be difficult to visualize using a routine hematoxylin and eosin stain. However if a dense core of amyloid is present (Figure 3a), amyloid plaques can be identified in the neocortex and hippocampus. Again, a silver stain preparation such as the Bielschowsky technique is the preferred staining method. Amyloid plaques are generally described as having three morphologic forms, including diffuse, neuritic and dense core[8] (Figure 3b). Diffuse plaques are poorly correlated with the degree of dementia and disease progression, and indeed are commonly found in the brains of non-demented elderly. Unlike NFTs, amyloid plaques accumulate mainly in the neocortex. In general the allocortex (including entorhinal cortex and hippocampus), the basal ganglia, relevant nuclei of the brainstem, and the cerebellum, are involved to a lesser extent and later than the association neocortex. Amyloid plaques usually involve all six layers of the neocortex, although layers I and VI are usually more spared than layers II–V. Clinicopathologic studies have shown that the amyloid plaque burden does not correlate with the severity or the duration of dementia.

Cerebral amyloid angiopathy: Cerebral amyloid angiopathy (CAA) is a vasculopathy with increasing incidence after the age of 60, and may occur in isolation (pure CAA), or more commonly in the context of Alzheimer's disease, with approximately 80% of Alzheimer's brains showing some degree of

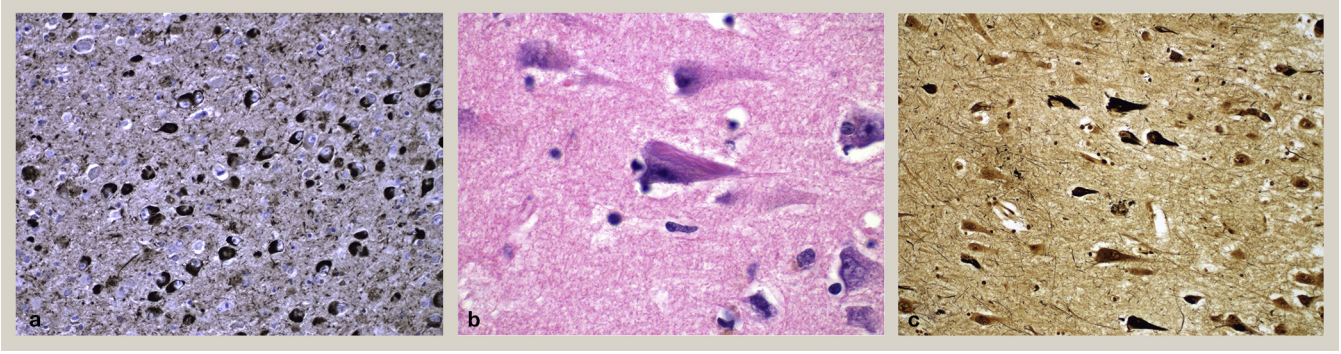

Figure 2 (**a**, **b**, **c**): Tau immunocytochemistry with many decorated neurofibrillary tangles (**a**). Hematoxylin and eosin (H&E) stain showing a characteristic, cytoplasmic neurofibrillary tangle with a fibrillar appearance, and pushing aside the nucleus (**b**). Bielschowsky silver impregnation stain showing several cytoplasmic silver positive lesions (**c**).

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