The review describes the histopathology and pathophysiology of Alzheimer’s disease.

Nearly a century ago, Alois Alzheimer described the first case of the disease that now bears his name. Alzheimer’s first encounter with this fateful case was in 1901, when a 51-year-old woman was admitted with aphasia, poor memory, lack of orientation, paranoid ideation, unpredictable behavior, hallucinations and severe cognitive deficits. After her death in 1906, Alzheimer reported the autopsy findings in a landmark presentation entitled, “On a Peculiar Disease Process of the Cerebral Cortex.” Alzheimer’s original pathological description of cerebral atrophy, neurofibrillary change and loss of neurons, remains remarkably accurate to this day.

Today, Alzheimer’s disease (AD) is recognized as the most common cause of dementia in the elderly, accounting for over 50% of cases. The most potent risk factor for AD is increasing age and the presence of the apolipoprotein ε4 allele. The lifetime risk of AD for an individual without the ε4 allele is 9%, while the lifetime risk of an individual carrying at least one ε4 allele is 29%. AD is more common among women than men with a ratio of 1.2 to 1.5. Other risk factors implicated in some studies include head injury, family history of dementia, lower income and occupational status and fewer years of education.

A clinical diagnosis of AD can be quite accurate in the hands of an experienced physician. Clinical workup includes screening for other causes of dementia in the elderly and exclusion of other etiologies (eg, hypothyroidism, drug-induced encephalopathy, chronic subdural hematoma, brain tumor). While neuropsychological testing, metabolic neuroimaging, and cerebrospinal fluid tau levels have been used to increase confidence in the probability that the dementia is due to AD, an unequivocal diagnosis of AD can be rendered only on neuropathological examination of brain tissue. By CT or MR imaging, there is evidence of cortical atrophy (notably the medial temporal lobe), with parietotemporal hypoperfusion on positron emission tomography (PET) and single photon emission computed tomography (SPECT). This selective early involvement of the medial temporal lobe is utilized in the diagnosis of AD by neuroimaging.

From a pathological perspective, the brain in AD is reduced in weight, with especially pronounced atrophy of the medial temporal lobe, and atrophy of the temporal, parietal and frontal association cortices. Primary
cortical areas (primary motor, sensory and visual cortex) and most subcortical structures are relatively preserved. The lateral ventricles are dilated secondary to cerebral atrophy. The hippocampus and amygdala are atrophic. The locus ceruleus often shows loss of pigment.

At a microscopic level, there is diffuse loss of large pyramidal neurons in the cerebral cortex in AD, especially involving the multimodal association cortices.$^6$ There is also neuronal loss in the hippocampus, amygdala, basal forebrain, and locus ceruleus. There is a substantial loss of synapses, which correlates with the degree of cognitive impairment. Concomitant with the cerebral atrophy, there is astrocytic gliosis.

Alois Alzheimer used the newly developed Bielschowsky’s silver staining method to demonstrate the neurofibrillary tangles in neurons of the cerebral cortex of his famous patient.$^1$ The Bielschowsky stain continues to be widely used to demonstrate AD pathology. Figures 1A and 1B illustrate the classical pathological findings in AD—neurofibrillary tangles and neuritic plaques in a section of cortex stained by the Bielschowsky stain.

The neurofibrillary lesions of AD present in the form of neurofibrillary tangles, neuropil threads, and neuritic plaques.$^{2,5,6}$ Neurofibrillary tangles are filamentous inclusions within the neuron body and proximal dendrites (Figure 1A). Whereas, neuropil threads (which have a thread-like appearance) are found in distal dendrites and axons.$^5$

At an ultrastructural level, neurofibrillary tangles are composed principally of paired helical filaments, which are intraneuronal proteinaceous structures composed of an abnormal form of the tau protein.$^{2,5,6}$ Paired helical filaments accumulate in neuronal cell bodies (neurofibrillary tangles), in neuronal processes throughout the cortex (neuropil threads), and in distended neuronal processes (dystrophic neurites) around the extracellular amyloid deposits in the neuritic plaque of AD.

Biochemically, neurofibrillary tangles are composed of a poorly soluble hyperphosphorylated as well as abnormally phosphorylated tau protein.$^7$ Normal adult tau is a soluble microtubule binding protein that is primarily localized in axons and plays an important role in the polymerization and stabilization of microtubules.$^5$ The abnormally phosphorylated tau of AD is less able to bind microtubules, presumably leading to microtubule depolymerization, disrupted axonal transport, compromised synaptic transmission, and ultimately neuronal death.$^5$

As shown in Figure 1B, another pathological hallmark of AD is the neuritic plaque. Neuritic plaques have a dense core of extracellular amyloid surrounded by an amyloid corona, in which dystrophic neurites (containing abnormal tau/paired helical filaments) and processes of reactive microglia are incorporated. Large numbers of neuritic plaques accumulate in the cerebral cortex in AD. Senile plaques of aging (nonneuritic senile plaques or diffuse plaques) are seen in elderly people without dementia—they lack the amyloid core, dystrophic neurites, and the inflammatory microglial response. On tissue sections, amyloid is demonstrated by the congo red stain or by fluorescence after thioflavin staining.

Other pathological findings on microscopy include Hirano bodies and granulovacuolar degeneration (GVD) in the neurons of the hippocampus (clear vacuoles pushing the cytoplasm and containing a basophilic granule). In some studies, the number of neurons affected by GVD correlated with the duration of dementia.$^2$ In AD patients, there is also cerebrovascular pathology with deposition of amyloid in blood vessels (cerebral amyloid angiopathy).

In AD, there is a highly selective distribution of neurofibrillary lesions and to a lesser extent of neuritic plaques. Regions most affected with neurofibrillary tangles are the medial temporal lobe, amygdala, the association cortices, and the nucleus basalis of Meynert. Within the entorhinal cortex, there is also a selective involvement of certain neuronal layers (layers II and IV) with relative sparing of layers III, V, and VI. It is noteworthy that the
large projection neurons in layers II and IV link the hippocampus with the association cortices. This disruption of the neural link between the hippocampus and the rest of the brain contributes to the amnesia in AD.

In terms of correlating pathology with clinical severity, there is a strong correlation between the density of neurofibrillary tangles and the severity of dementia (specifically neurofibrillary tangles in the neocortical as-

Figures 1A and 1B. Section of cerebral cortex stained by the Bielschowsky stain demonstrating neurofibrillary tangles (arrowheads) (A, high power view) and several neuritic plaques (arrowheads) (B, medium power view).
Correlations between senile plaques and dementia have been more controversial, but mature neuritic plaques with an amyloid core do correlate with dementia, albeit not as strongly as neurofibrillary tangles.5

The neurofibrillary tangles and neuritic plaque lesions of AD are accompanied by an inflammatory reaction including proliferation of microglia and astrocytes, prompting research into the role of anti-inflammatory medication in AD.2

Several neurotransmitter systems are affected in AD. There is a severe loss of cholinergic neurons in the nucleus basalis of Meynert of the forebrain.5 Abnormalities of the cholinergic systems form the basis of pharmacotherapeutic interventions aimed at enhancing cholinergic activity. Cholinesterase inhibitors are the only medications approved by the U.S. Food and Drug Administration as treatment for AD.3 In addition to cholinergic neurons, other neurotransmitter systems are also affected including the locus ceruleus (norepinephrine) and the raphe nuclei (serotonin).5

The amyloid protein in the neuritic plaques and vessels in AD is beta-amyloid (beta/A4 protein, amyloid β-peptide). It is derived from a larger protein, the A4 (amyloid precursor protein or APP), encoded by a gene on chromosome 21.2,8 The amyloid β-peptide was first sequenced from meningeal blood vessels of patients with AD and individuals with Down's syndrome.9 Subsequently, the same peptide was found in the neuritic plaques of AD, launching a new era of AD research, which culminated in the cloning of the APP gene and its localization to chromosome 21.9 It is noteworthy that individuals with trisomy 21 (Down's syndrome) invariably show AD type neuropathology. According to the amyloid hypothesis of AD, accumulation of amyloid β-peptide in the brain is the primary influence driving AD pathogenesis.9

Mutations account for less than 5% of all cases of AD.3 In familial AD, mutations of the gene encoding APP (APP gene, chromosome 21) have been found.3 Other mutations have been found to involve genes on chromosome 14 (presenilin-1 gene) and chromosome 1 (presenilin-2 gene).3

A problem in terms of a diagnosis based on tissue pathology alone is the fact that the microscopic lesions of AD may occur to a minimal or modest degree in nondemented elderly people. As a practical guide, the finding of neurofibrillary tangles in a neocortical brain biopsy allows for a relatively certain diagnosis of AD.2 If neurofibrillary tangles and neuritic plaques are abundant throughout the neocortex and the hippocampus at autopsy, then a neuropathologic diagnosis of AD is relatively straightforward.2 Neurofibrillary tangles without neuritic plaques are also encountered in a number of other “tauopathies” such as supranuclear palsy and dementia pugilistica,2,7 but a combination of tangles, neuritic plaques, vascular amyloid, and granulovacular degeneration is diagnostic of AD.

This article is intended only as a brief overview of the pathology and does not represent an exhaustive review of the pathological or clinical literature on the subject.

REFERENCES