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Research Paper

Alzheimer's Disease Neuropathological Diagnosis

Dr.Tshetiz Dahal
General Physician/Clinical Researcher and Writer
Lugansk State Medical University, Luhansk Oblast, 93000, Ukraine

ABSTRACT
Although less prevalent clinical manifestations are gradually recognized, Alzheimer's disease is a progressive neurodegenerative illness most frequently linked with memory problems and cognitive decline. The presence of these amyloid plaques and neurofibrillary tangles is still necessary for a clinical diagnosis today despite the fact that the disease's key pathological characteristics have been understood for more than a century. Globally, Alzheimer's disease is the most frequent cause of dementia. For the vast majority of patients, there are still no viable treatment options available, and other than a limited number of family cases caused by genetic mutations, the disease's principal causes are still unknown. The knowledge that Alzheimer's disease is a mixed proteinopathy (amyloid and tau) usually coupled with other age-related diseases such as cerebrovascular disease and Lewy body disease complicates efforts to create efficient diagnostic tools and disease-modifying therapeutics. Research is still being done to clarify the connections and interaction of diverse co-pathologies. This article describes the pathologic characteristics of Alzheimer's disease that are associated with aetiology as well as those that are unavoidable findings of ambiguous relevance, like granulovacuolar degeneration and Hirano bodies. There is also discussion of additional disease processes that are common but not always present, such as pathologic diseases that can exhibit clinical similarities to Alzheimer's disease. These include argyrophilic grain sickness, TDP-43 proteinopathies, Lewy body disease, and cerebrovascular illness. An overview of the pathophysiology of Alzheimer's disease, its defining pathologic substrates, and the associated pathologies that may have an impact on diagnosis and treatment are provided in this article.

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ABBREVIATIONS
AD: Alzheimer's Disease, **AGD:**Argyrophilic Grain Disease, **APOE:** Apolipoprotein E, **APP:** Amyloid Precursor Protein, **ARTAG:** Aging-related Tau Astrogliopathy, **CAA:** Cerebral Amyloid Angiopathy, **DLB:** Dementia with Lewy Bodies, **EOAD:** Early Onset Alzheimer's disease, **FAD:** Familial Alzheimer's, **GVD**: Granulovacuolar Degeneration, **LOAD:**Late Onset Alzheimer's disease, **MID:**Multi-infarct Dementia, **NFT:**Neurofibrillary Tangle, **PART**:Primary Age-related Tauopathy, **PCA:**Posterior Cortical Atrophy, **SVD**:Small Vessel Disease.

I. Historical information

More than a century ago, Alois Alzheimer initially described the neurodegenerative condition that would later take his name. Today, the clinical diagnosis of this condition still requires the presence of the amyloid plaques and neurofibrillary tangles he described [1]. The most prevalent type of dementia is Alzheimer's disease (AD), a progressive neurological illness most frequently characterized by initial memory loss and cognitive decline that can eventually impact behaviour, speech, visuospatial orientation, and the motor system [2]. This conventional presentation is not invariably followed by variant syndromes with early localised atrophy, and pathological subgroups of AD have been identified [3]. The only reliable way to diagnose clinical AD dementia is by post-mortem neuro-pathologic analysis, but research centres that can measure the amyloid and tau burden in patients while they are still alive are challenging this long-held belief [4]. Additionally, a protracted asymptomatic preclinical phase and the possibility of the disease in people with normal cognitive function are characteristics of AD [5]. In addition, other neurodegenerative co-pathologies are rarely present in AD cases, as shown in Table 1's analysis of Mayo Clinic Brain Bank data. It is thought to be a typical aspect of ageing since it is so closely linked to old age [6]. Alzheimer's disease currently has no disease-modifying medicines [7].

TABLE 1 :1153 patients with an AD pathologic diagnosis had comorbidities. Pathologic comorbidities were found in the majority of AD cases in the Mayo Clinic Brain Bank from 2007 to 2016. Additional pathologies beyond the primary and secondary diagnoses given are indicated by a plus sign (+) in the section on the pathological diagnosis of AD. (Student t-Test, p 0.01) Bold indicates significance from the only AD cases.

Pathological Dx	Cases (n)	Age (yr)	Brain (g)	Braak	Thal
AD	243	76.5 ± 10.8	1077 ± 159	5.5 ± 0.7	4.7 ± 0.6
AD/LBD	175	76.0 ± 10.2	1053 ± 151	5.6 ± 0.6	4.8 ± 0.6
AD/LBD+	206	81.8 ± 9.3	1025 ± 170	5.6 ± 0.6	4.8 ± 0.5
AD/Vas	113	84.5 ± 7.9	1070 ± 164	5.3 ± 0.8	4.6 ± 0.8
AD/Vas+	77	86.0 ± 6.4	1043 ± 142	5.3 ± 0.7	4.8 ± 0.6
AD/CAA	42	76.1 ± 11.6	1089 ± 163	5.6 ± 0.6	4.6 ± 0.6
AD/CAA+	110	80.1 ± 9.0	1086 ± 163	5.6 ± 0.6	4.7 ± 0.7
AD/HpScl	27	86.0 ± 6.9	1088 ± 158	5.4 ± 0.7	5.0 ± 0.0
AD/HpScl+	51	87.8 ± 6.9	1012 ± 174	5.4 ± 0.7	4.8 ± 0.6
AD/Other	59	79.3 ± 10.9	1044 ± 164	5.4 ± 0.8	4.7 ± 0.7
AD/Other+	50	81.9 ± 11.2	1019 ± 186	5.4 ± 0.8	4.5 ± 0.8

Epidemiology

Dementia is thought to impact more than 47 million people worldwide, and as of 2018 [8], it was projected that these illnesses would cost more than $1 trillion annually. With 60 to 80 percent of cases being AD, it is the most prevalent type of dementia. Less than half of these cases are projected to be pure AD, while the remainder are anticipated to be mixed dementia's [9]. Each of these causes accounts for between 5 and 10 percent of cases of dementia. Of these, vascular dementia and Lewy body dementia are most frequently linked to mixed pathology, including concurrent AD [9]. Other common causes of dementia include Parkinson's disease with dementia, frontotemporal lobar degeneration, and normal pressure hydrocephalus. As the population ages, it is predicted that more than 131 million people would be impacted by these crippling and financially crippling diseases by the middle of the century [8]. The greatest risk factor for AD is ageing, with the incidence of all dementia's doubling every 6.3 years from 3.9 per 1000 for those between the ages of 60 and 90 to 104.8 per 1000 for people over the age of 90 [10]. According to estimates from two sources, prevalence ranges from 10% for people over 65 to 40% for people over 80 [2]. Effective pre-clinical diagnosis and treatments are required to arrest disease progression before symptoms appear due to the skyrocketing personal and financial expenses.

Etiology

Amyloid precursor protein (APP), presenilin 1 (PSEN1), or PSEN2 gene mutations can result in dominantly inherited familial AD (FAD). Less than 1% of instances of AD are caused by these uncommon familial variants. The typical age of onset for FAD is 46.2 years [11], although it can appear as early as 20 years old. Affected individuals under the age of 65 are said to have early onset Alzheimer's disease (EOAD), which is slightly more common than FAD cases but only makes up less than 5% of all cases of AD with a pathology diagnosis. The course and presentation of EOAD are frequently aggressive [12]. Similar to Down's syndrome patients, most Down's syndrome patients with a partial or full chromosome 21 trisomy, which includes the region of chromosome 21 where APP is located, have Alzheimer type pathology by the age of 40, with many developing clinical symptoms after the age of 50. The majority of these patients have dementia by the age of 65 [14]. Although genetic risk factors, most notably the apolipoprotein E gene (APOE), have been found, late onset AD (LOAD), which is more prevalent, is still thought to be sporadic [7]. The highest risks of acquiring AD include age, family history in a first degree relative, and APOE4 genotype [14]. The risk ratio for AD in people with a single copy of the APOE4 polymorphism is 3 compared to non-carriers. The chances ratio for those who are homozygous for APOE4 is 12 [7]. Additionally, the APOE4 allele seems to increase the risk of traumatic brain damage, Down's syndrome, Lewy body dementia, and vascular dementia [15]. Genome-wide association studies have implicated nearly 30 genes, including TREM2, ADAM10, and PLD3, as additional risk factors for LOAD. These genes not only directly affect APP and tau but also regulate cholesterol metabolism, endocytosis, and immune response among those with known functions [16, 17]. Understanding the function of existing and newly discovered risk factors ought to shed light on the pathophysiological mechanisms behind Alzheimer's disease.

Pathology of Alzheimer's Disease

Macroscopic Features

The suitable technique of diagnosis for AD is still pathologic. On macroscopic examination, certain characteristics of AD can be identified, but no single characteristic or set of characteristics can be used to diagnose AD. However, some characteristics are very suggestive of AD. The multimodal association cortices and limbic lobe components exhibit the most pronounced cortical atrophy in the AD brain, which is frequently at least moderate. While primary motor and somatosensory cortices frequently appear intact, the frontal and temporal cortices frequently exhibit increased sulcal gaps with atrophy of the gyri [18]. Due in part to functional imaging studies [19, 20], there is growing acknowledgment of atrophy in posterior cortical areas in AD, most notably the precuneus and posterior cingulate gyrus. As a result of this atrophy, the frontal and temporal horns of the lateral ventricles frequently expand, as seen in Fig. 1, and decreased brain weight is seen in the majority of affected people. None of the macroscopic characteristics are unique to AD, and clinically healthy individuals who are not affected by AD may experience mild cortical atrophy, notably in the frontal lobes, with volume loss primarily impacting white matter [21]. While it is a hallmark of AD [18, 22, 23], medial temporal atrophy affecting the amygdala and hippocampus and typically accompanied by temporal horn expansion can also be found in other age-related illnesses including hippocampal sclerosis or argyrophilic grain disease.The decrease of neuro-melanin pigmentation in the locus coeruleus, as seen in Fig. 1 [23], is another macroscopic characteristic frequently seen in AD. None of these findings stand alone as being unique to AD, but they frequently lend strong support nonetheless, especially in the absence of macroscopic alterations unique to other neurodegenerative conditions.

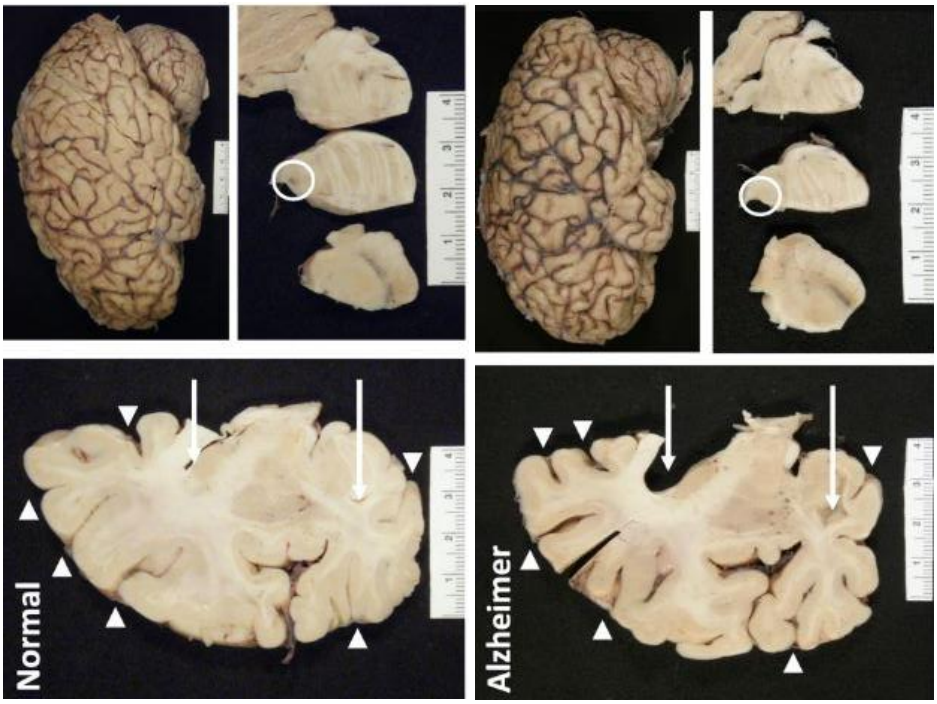

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FIGURE 1 : Gross Anatomy of Alzheimer's Brain. Lateral view of an Alzheimer's brain can show widening of sulcal spaces and narrowing of gyri compared to a normal brain.

This may be more readily observed in coronal sections as indicated by the arrowheads, and this atrophy is often accompanied by enlargement of the frontal and temporal horns of the lateral ventricles as highlighted by the arrows. Additionally, loss of pigmented neurons in the locus coeruleus is commonly observed in the pontine tegmentum as shown with the open circle. None of these features is exclusive to Alzheimer's disease.

Microscopic Features

The form, density, and spatial distribution of lesions are used to make the diagnosis of AD, which is based on microscopic analysis of various brain regions using staining procedures that can identify Alzheimer type neuropathologic alteration [24]. Numerous brain areas that are susceptible to pathologic changes of the Alzheimer type are also susceptible to other disease processes, including -synucleinopathy and TDP-43 proteinopathy. Mixed pathologies are typical. In fact, the majority of AD cases in the Mayo Clinic Brain Bank

from 2007 to 2016 (Table 1, Additional file 1: Figure S1) had concurrent non-Alzheimer diseases, and the number of comorbidities rose with age. In addition, it is evident from a review of the initial clinical diagnoses for cases with pure AD pathology (Table 2, Additional file 2: Figure S2) that a number of clinical syndromes can mimic Alzheimer's disease.

TABLE 2 : Clinical Diagnoses of 227 Patients with a Pathologic Diagnosis of Pure AD.
More than a third of pathologic AD cases on the Mayo Clinic Brain Bank from 2007 to 2016 were not expected to have AD. Plus sign (+) in the column on clinical diagnosis indicates additional clinical diagnoses are supported. Bold indicates significance differences from the pure AD cases (Student t-Test, $p < 0.01$)

Clinical Dx	**Cases (n)**	**Age (yr)**	**Brain (g)**	**Braak**	**Thal**
AD	109	77.3 ± 11.2	1061 ± 163	5.5 ± 0.7	4.7 ± 0.7
AD+	35	73.0 ± 8.5	1069 ± 138	5.6 ± 0.6	4.8 ± 0.5
LBD	16	80.9 ± 9.8	1073 ± 158	5.3 ± 0.6	4.5 ± 0.8
CBS	12	71.3 ± 7.4	1008 ± 169	5.9 ± 0.3	5.0 ± 0.0
FTD	10	66.4 ± 8.9	1103 ± 128	5.5 ± 1.1	4.9 ± 0.4
Aphasia	06	72.2 ± 7.1	940 ± 109	5.9 ± 0.2	4.8 ± 0.4
Other	21	78.2 ± 10.3	1132 ± 155	5.4 ± 0.8	5.0 ± 0.0
MCI	11	87.7 ± 6.9	1162 ± 136	4.9 ± 0.6	5.0 ± 0.0
Normal	07	85.9 ± 6.6	1251 ± 120	4.7 ± 0.8	3.0 ± 0.0

It has been known since more than a century ago [25] that external amyloid plaques and intracellular neurofibrillary tangles are necessary for diagnosis. Additionally, tau-positive neuropil threads, dystrophic neurites, activated microglia, and reactive astrocytes can also be seen. Also frequent [18, 23] are eosinophilic Hirano bodies, granulovacuolar degeneration (GVD), and cerebral amyloid angiopathy (CAA). These lesions cause the loss of synapses and neurons in areas that are vulnerable, which causes the symptoms of AD that are most frequently seen. According to the available data, structural alterations in the brain, such as hippocampal volume reduction and reduced glucose metabolism, can occur decades before amyloid deposition and tau pathology in AD [26]. Downstream clinical characteristics of memory loss, social dependence, and motor impairments gradually show as the disease advances [5, 6].

In other AD subtypes, the typical symptoms of early AD (such as memory problems) may alter, and clinical signs in fact lack specificity for a pathologic process, instead indicating brain regions or systems affected by the disease process [3, 4]. This conclusion is underscored by the fact that 3 percent of patients with their last clinical exam were deemed clinically normal, and 29% of those with pathological evidence of high likelihood Alzheimer's disease [24] were judged to have other conditions (Table 2).

Amyloid Plaques

According to Alzheimer in his description of Alzheimer's disease and originally that same year by Oskar Fischer, senile amyloid plaques, also known as "miliary foci," are extracellular, nonvascular accumulations of the peptides Aβ-40 and Aβ-42 that are produced as a result of abnormal processing of the amyloid precursor protein by the β- and γ- secretases and an imbalance in the production and clearance pathways [1, 27,28,29]. These little 4 kDa peptides (A4) fold into extremely fibrillogenic beta-pleated sheet structures. When exposed to polarized light, the Aβ filaments bind congophilic dyes and exhibit the characteristic amyloid birefringence [30]. Studies using antibodies to the A4 protein—now known as Aβ peptides—showed that they are involved in the early development of amyloid plaques, which are not detected by congophilic dyes.[31]. Additional Aβ peptides containing between 38 and 43 amino acids are also detected, but Aβ42 is the most fibrillogenic and the predominant component of amyloid plaques in AD [6]. There are many reviews describing the generation of Aβ peptides [32], and these pathways remain viable therapeutic targets. The terminology for Aβ amyloid plaques can be confusing. Nearly a dozen types of nonvascular amyloid deposits have been described, but the two types of amyloid plaques most commonly observed in AD are diffuse plaques and dense core plaques [29, 33] as shown in Fig. 2a, b [23, 29]. Diffuse plaques form initially in the neuropil and stain weakly by thioflavin S and other amyloid binding dyes (e.g., Congo red).

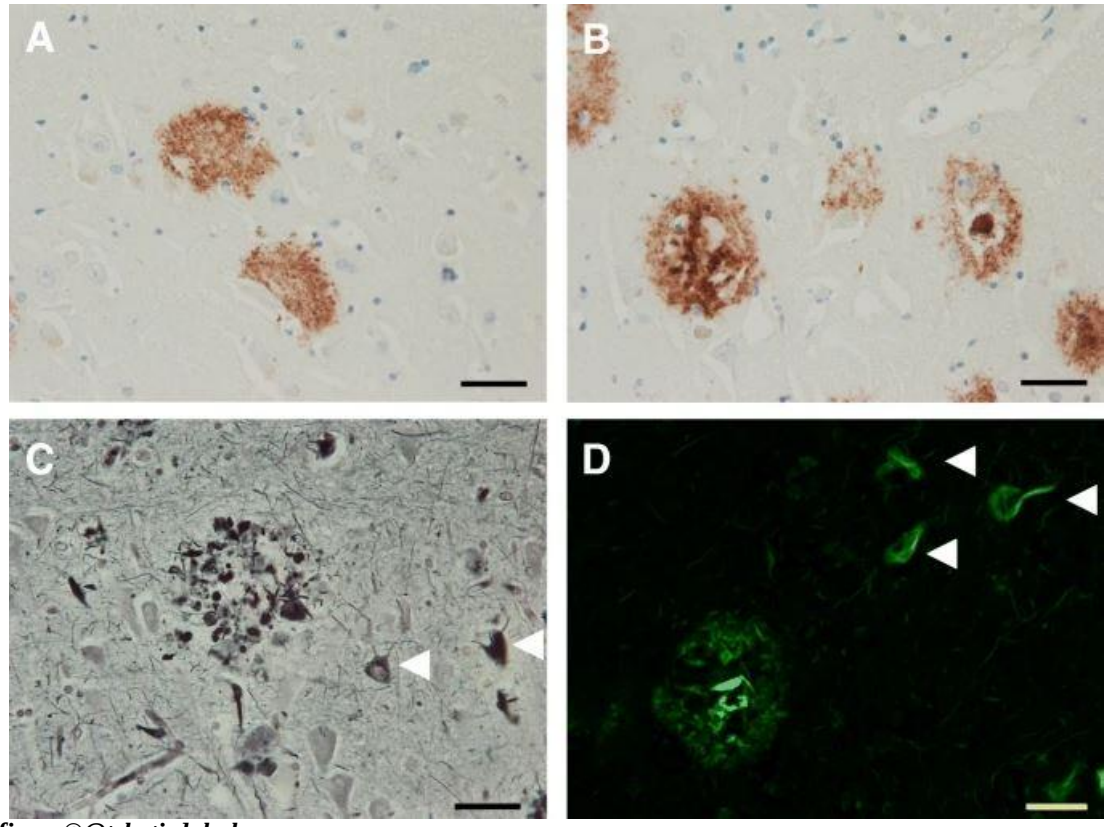

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FIGURE 2 : Alzheimer Senile Plaques. Immunohistochemistry of affected Alzheimer's tissues using antibodies directed against Aβ peptides demonstrates the presence of both diffuse

(a) and dense core
(b) senile plaques. These dense core plaques are often associated with neuritic elements that can stain filamentous tau and correlate with disease severity. Neuritic AD plaques are readily observed using Bielchowsky silver staining
(c) or Thioflavin S staining
(d). These stains can also label neurofibrillary tangles as shown by the arrowheads. The scale bars are 40 μm

They commonly lack argyrophilia on Bodian silver stains, and they do not show preferential accumulation of activated microglia and reactive astrocytes. In comparison, dense core plaques have dense reticular or radiating compact dense amyloid and are intensely positive with thioflavin S fluorescent microscopy and Congo red, suggesting they contain more fibrillogenic forms of Aβ [29, 34, 35]. More importantly, a subset of dense core plaques have neuritic elements as shown in Fig. 2c, d, and these cored neuritic plaques (NPs) can be associated with tau-positive or dystrophic neurites, the latter demonstrated with a variety of markers including synaptic and APP immunohistochemistry [33]. Dense cored NPs are also accompanied by synaptic loss, activated microglia and reactive astrocytes [23, 29, 36]. In contrast, diffuse plaques often lack neuritic components, though diffuse neuritic plaques can be observed in advanced AD [33]. The diffuse plaques are positive with Aβ immunohistochemistry and contain filamentous Aβ at the ultrastructural level, but it is not certain whether diffuse plaques are a part of pathological aging or an early stage in the maturation of neuritic Aβ plaques [29]. Indeed, it appears as many as 8 types of nonvascular amyloid plaque deposits can form after initial deposition of Aβ and that the morphology and type of plaques can vary from region to region [29]. Plaques composed almost exclusively of dense cores lacking neuritic components have been termed "burnt out" plaques [18]. Most importantly the neuritic plaques with dense amyloid and tau-positive neurites are believed to be closely associated with neuronal loss and cognitive decline in Alzheimer's disease [37, 38].

Neuritic Plaques

Cored neuritic plaques with tau-positive neurites typically feature a zone of thick amyloid in the centre, which can occasionally form a compact core. The concept that A causes neuronal degeneration and cognitive loss in AD is supported by the dense core's ability to show radiating A fibrils and the concentration of

dystrophic neurites and activated microglia in these plaque's periphery zones [18, 39]. Activated microglia and reactive astrocytes are typically seen in neuritic plaques, and their processes regularly mix with neuritic components at the plaque's periphery. Tau filaments are seen in some of the dystrophic neurites connected to neuritic plaques, and electron microscopy has shown that these filaments can have a paired helical filament form [23]. According to research [29, 36], these "type 1" dystrophic neurites are thought to form in areas that receive input from neurons with neurofibrillary tangles in their soma. Neuritic plaques contain a variety of dystrophic neurites [36]. Some dystrophic neurites also include neurofilament proteins in addition to tau-positive neurites, indicating that cytoskeletal alterations are a component of the neurodegenerative process [40]. Additionally, a subgroup of plaque-associated dystrophic neurites can contain degenerating mitochondria, lysosomal bodies, and vesicles, some of which have ubiquitin-immunoreactivity, suggesting that trafficking and protein degradation pathways are impacted [23]. In a cell culture model, more recent investigations have shown that exogenous A fibrils cause cell death and membrane integrity to be disrupted [41]. In fact, even the existence of dystrophic neurites, which are thought to be benign age-related neurites, offers proof that amyloid plaques have a detrimental effect on the integrity of the neuronal processes nearby [36]. Although diffuse amyloid plaques with neuritic elements are seen in advanced disease, their disease relevance and relationship to the formation of dense core neuritic plaques is unknown [33]. While dense core neuritic plaques are thought to be more closely associated with neuronal loss in AD [38], diffuse amyloid plaques with neuritic elements are observed in early disease. Research is still being done to better understand the connections between amyloid-driven neuritic disease, more widespread tau neuronal and thread pathology, and neuronal loss.

Distribution of Amyloid Plaques

Numerous staging systems have been developed as a result of the tendency of senile plaque and neurofibrillary tangle formation in AD to form neuro-anatomically in stereotypical patterns [42, 43]. Heiko and Eva Braak made one of the initial proposals to stage amyloid plaques in AD. There was a three stage plan put forth, with Stage A affecting the basal frontal and temporal lobes, Stage B extending into the association neocortices and hippocampus, and Stage C affecting the main cortices, subcortical nuclei, and cerebellum [42]. Layers III and Va of the cortical levels are most affected, followed by Layers IV and Vb, whereas other layers were largely unaffected [42]. Dietmar Thal, a research partner of Braak's, updated the staging of the Braak plaque more recently, and the NIA-AA [44] and BrainNet Europe [45] have adopted this system of amyloid "phases" employing very sensitive silver staining or A antibodies. Neocortex involvement first appears in Thal Phase 1, followed by allocortex participation in Phase 2, subcortical nuclei, including the striatum, in Phase 3, brainstem involvement in Phase 4, and cerebellar involvement in Phase 5 [43]. Phases 1-4 can be identified for practical purposes by amyloid accumulation in the medial temporal lobe [29]. Neurologically healthy patients frequently exhibit the Thal 1-3 amyloid phase, as demonstrated in Table 2.

Cerebral Amyloid Angiopathy (CAA)

Aβ peptides can build up in cerebral blood vessels as well as in the brain parenchyma as amyloid plaques. An estimated 85–95 percent of AD sufferers exhibit cerebral amyloid angiopathy to some extent. According to Table 1 in the Mayo Brain Bank, moderate-to-severe CAA affects 13% of confirmed AD patients, which may be verified using Aβ immunohistochemistry or thioflavin S fluorescence microscopy (Figs. 3a, b) [46]. Amyloid deposits can damage tiny arteries, arterioles, and even capillaries in the grey matter of cerebral cortices and in leptomeningeal vasculature and are enriched in Aβ40 in CAA (whereas parenchymal deposits are enriched in Aβ42 species) [18, 23]. In actuality, there are two different kinds of CAA. Small arteries, capillaries, and arterioles are all affected by type 1 CAA, which is four times more likely to be linked to APOE4. Type 2 CAA is two times more likely to be related with APOE2 and affects arterioles and small arteries but not capillaries [47, 48]. Interestingly, leptomeningeal arteries are more fragile than parenchymal vessels, and the parietal and occipital cortices are more vulnerable than the frontal and temporal lobes [23]. The frontal and occipital lobes are often affected by lobar haemorrhage caused by severe CAA, which can reduce blood flow and cause ischemic lesions or minor infarcts [18]. The prevalence of CAA in AD and its link to beginning at a younger age support its participation in the disease process, independently influencing clinical manifestations of AD. [46, 49, 50]. Imaging approaches are being developed to distinguish CAA from plaque amyloid, and a number of methodologies have been proposed to assess the severity of CAA burden [46]. It's interesting to note that vaccination methods that target Aβ-peptides may be effective in reducing the burden of amyloid plaques while converting amyloid into CAA, which is occasionally linked to inflammation and bleeding [51, 52]. Animal model research suggests that neuronal Aβ is the source of capillary CAA, which results in decreased perivascular clearance, peri-capillary Aβ deposits, and eventually CAA [53]. The risk of APOE4 for capillary CAA is thought to be related to less effective transendothelial clearance of Aβ-apolipoprotein complexes compared to complexes in APOE2 carriers [48]. It's interesting to note that perivascular Aβ accumulation and

the degree of perivascular neuritic tau pathology coincide, suggesting that amyloid deposition is the primary cause of dystrophic neurites [54].

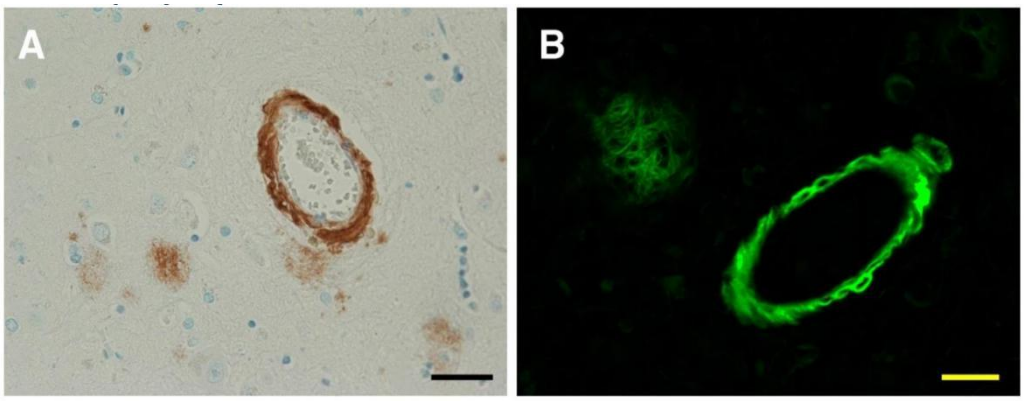

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FIGURE 3 : Cerebral Amyloid Angiopathy. Cerebral amyloid angiopathy or congophilic amyloid angiopathy can by visualized in frontal cortical sections using Aβ directed immunohistochemistry.

(a)

(b) or Thioflavin S staining.

(c) similar to that used to detect senile plaques, and they are believed to contribute independently to the Alzheimer's disease course. Scale bars are 40 μm.

Neurofibrillary Tangles and Neuropil Threads

In the foundational work by Alzheimer, "neurofibrils," which formed thick bundles close to the cell surface of afflicted neurons, were initially identified as neurofibrillary tangles (NFTs) [25]. These were identified using the Bielschowsky silver stain, and as shown in Fig. 4a [1], they were related to neuronal death and disintegration, resulting in what are now known as extracellular or "ghost tangles." Both amyloid plaques, particularly cored neuritic plaques, and neurofibrillary tangles made of filamentous tau proteins are necessary for a neuropathologic diagnosis of AD. According to data, the later lesions have a stronger correlation with cognitive impairment than amyloid deposits [55]. According to electron microscopy observations, the tau filaments in AD exhibit clear periodicity and have been dubbed "paired helical filaments" (PHFs) [56]. They appear to be made up of two smaller filaments, each about 10 nm in diameter, that twist around one another to form periodic structures with a crossover distance of 65–80 nm. These filaments, as seen in Fig. 5, vary in width between roughly 10 and 20 nm, and their homogeneity has made it possible to resolve the structural folding of the core peptide using cryoelectron microscopy at 3.5 A [57]. Additionally, AD shows the presence of straight filaments (SFs), however these show less periodicity, a greater crossover distance, and width variations between 10 and 15 nm [58]. Straight helical filaments that are uniformly 10 nm in diameter and found in various tauopathies as well as filaments produced in vitro using recombinant tau are distinct from the straight helical filaments found in Alzheimer's disease. All 6 tau protein isoforms, including those with 3 repeats (3R tau) and 4 repeats (4R tau) in the microtubule binding region, are present in PHF in AD. PHF's core is the repetitive domain [59]. Compared to unassembled, normal tau, AD tau proteins are hyperphosphorylated, irregularly folded, and lack the ability to bind and stabilize microtubules in the axon properly [60]. This decrease in tau function is accompanied by an increase in the abnormal tau's aggregation properties. The ability of PHFs to co-aggregate with regular tau proteins is hypothesized to result in both a loss of normal function and a toxic gain in function [61]. Neuropil threads (NTs), which are dendritic and axonal components containing filamentous tau, also contain PHFs and SFs made of tau protein. The majority of the tau burden in AD may be made up of neuropil threads, which are believed to come from NFT-containing neurons [62,63,64]. It is believed that tau pathology in AD may extend across the brain due to the corruption of normal tau.

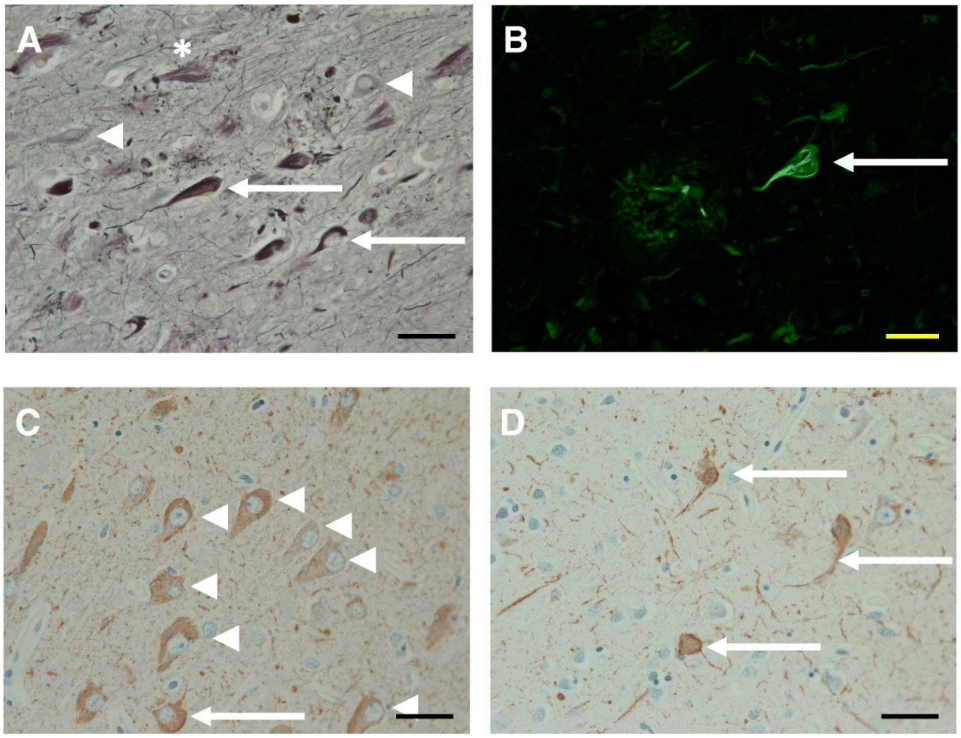

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FIGURE 4 : Neurofibrillary Tangles. Neurofibrillary tangles develop from intracellular pre-tangles containing misfolded tau and small tau aggregates to mature NFTs containing bundles of cross-linked tau filaments before the neuron dies and an extracellular ghost tangle (asterisk) remains. Silver staining (a) and Thioflavin S
(d) capture many mature tangles (arrows) and some pre-tangles (arrowheads) along with amyloid plaques and tau neuropil threads. Development of NFTS from the pre-tangles is more easily visualized using tau immunohistochemistry
(c). This allows the mis-localized somal tau to be distinguished readily from the bundles of PHFs in NFTS in addition to the neuropil threads that can also be pronounced
(d). The scale bars are 40 μm

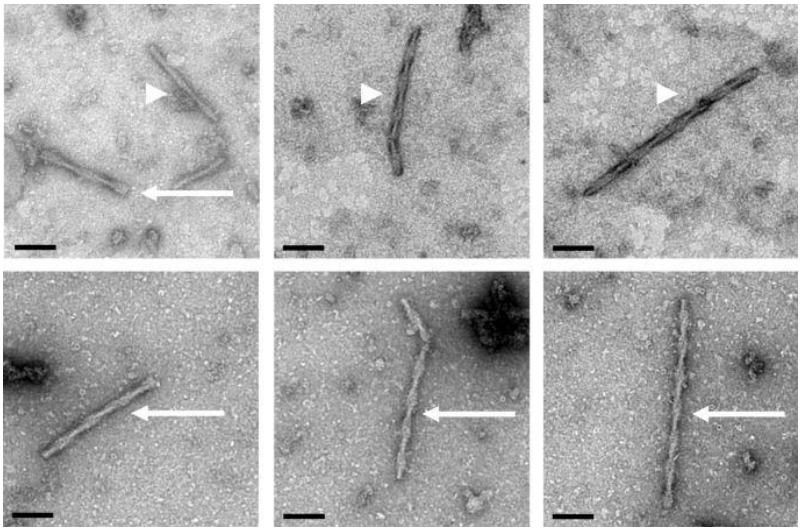

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FIGURE 5 : Paired Helical Filaments and Straight Filaments. Neurofibrillary tangles are composed of insoluble tau filaments that can be extracted using detergents or acids and visualized using electron microscopy and negative staining such as 2% uranyl acetate here. The paired helical filaments (arrows) and straight filaments (arrowheads) both appear to be composed of pairs of 10 nm filaments that wrap around one another with the PHFs exhibiting wider 10–20 nm modulations in diameter and the SFs narrower 10–15 nm modulations. Length bars are 100 nm.

Distribution of Neurofibrillary Tangles

Traditional histological or histofluorescent staining techniques, such as the Bielschowsky silver stain or thioflavin-S, can be used to detect neurofibrillary tangles. More recently, immunohistochemistry approaches using antibodies against tau have also been used. Numerous neuropil threads that are thought to be a component of the neuronal degeneration linked to neurofibrillary tangle development are also marked using these techniques [23]. In the cell body and dendrites of neurons, neurofibrillary tangles first appear as "pretangles" containing aberrant tau conformers (but not polymerized into tiny aggregates). These develop in the perikarya and proximal cell processes into aggregated filaments. In addition to other locations, they can show up as "globose tangles" in the basal nucleus of Meynert, raphe nuclei, substantia nigra, and locus coeruleus as well as "flame shaped tangles" in the pyramidal neurons of the hippocampus and layer V of the association cortices. The type of neuron in which the tangle arises determines its shape [18]. The neurons eventually perish as a result of the mature tangles displacing the nucleus and other essential cellular components. The insoluble filaments are left in the extracellular spaces, where they form a "ghost tangle" with extracellular proteins (such Aβ), microglia, and astrocytes.

It is believed that neuronal tau pathology, leading to tangles and neuropil threads, is linked to neuronal death and cognitive decline in AD. Studies have shown that their number and location correlates with neuronal loss, disease severity and clinical course [65, 66]. The relationship of neurofibrillary tangles to cell death is not understood, though mutations in the tau gene (MAPT) on chromosome 17 lead to tau accumulation and neuronal loss in other neurodegenerative diseases. These disorders are termed frontotemporal dementia with Parkinsonism linked to chromosome 17 [67]. Unresolved is whether these associations stem from either, both, or neither of these disorders' loss of microtubule integrity and tau function. It is still debatable whether tangles interfere with protein homeostasis or sequester essential cellular components. The development of tangles often follows a stereotypical pattern, much like plaque accumulation in AD.

Heiko and Eva Braak proposed the most popular staging strategy for tangling in 1991 [68]. The neuropathologic criteria for AD frequently use the staging system [69, 70]. The transentorhinal cortex, which connects the temporal isocortex to the allocortical entorhinal cortex, exhibits tangles during the first phases of NFT deposition in Braak Stage I. The multipolar neurons from the entorhinal cortex here in the transentorhinal cortex change into pyramidal cells like those in the nearby temporal isocortex as the superficial entorhinal Pre-layer deepens in position. Along with the sporadic tangles seen in the CA1 sector of the hippocampus, particular nuclei in the basal forebrain, and the thalamus, it is these Pre-projection neurons of the transentorhinal cortex that acquire the earliest NFTs in Alzheimer's disease [68, 71]. NFTs that were shown in Stage I become more robust in Stage II, and the Pre-layer of the entorhinal cortex becomes involved as well as having a stronger representation in the thalamic anterodorsal nucleus. The first two phases of NFT and NT development are known as the "transentorhinal stages," and NFTs are few in the isocortex and almost nonexistent in the hippocampus itself. All previous pathology becomes more robust during Stages 3–4 termed the “limbic stages,” and isocortical pathology remains limited with primary motor and sensory cortices markedly untouched. In Stage V the Pre-β and Pre-γ layers and most of the hippocampus are now affected, and NTs and ghost tangles become more pronounced in previously affected areas and NPs can be seen in CA1. The largest changes involved in Stage V regard the extensive involvement of the isocortex. In mild cases this may be more apparent in the basal portion of the medial frontal and the inferior portions of the temporal and occipital lobes followed by areas of the insula and the orbitofrontal cortex. Even though layer III of the primary motor and sensory cortices only occasionally exhibits NPs, more severe cases involve the majority of the association cortices, including the temporal lobes. In Stage VI, previously damaged areas keep getting worse until all associated areas are badly damaged. Primary motor cortex pathology is still mostly limited to layer III NPs, while changes in the primary sensory cortex are marked by frequent NTs and sporadic NFTs in layer V. A greater amount of the striatum, substantia nigra, hypothalamus, and anteroventral and reticular nuclei of the thalamus are also engaged. These stages make up the "isocortical stages," together with Stage V.Recent modifications of the Braak scheme also consider possible earlier involvement of subcortical nuclei (e.g., locus ceruleus) [68, 72].

Granulovacuolar Degeneration

In AD, other pathologic alterations are unavoidably seen, but they are less well understood in terms of their clinical significance. One of these observations is granulovacuolar degeneration. In addition to AD, it is also discovered, albeit in low density, in some healthy elderly people and in other neurodegenerative illnesses. Alzheimer and colleagues initially characterized these intraneuronal vacuoles in 1911, and they are now regarded to be a crucial part of AD [73,74,75]. As seen in Fig. 6a, they are 3-5 m vacuoles with a core 0.5–1.5 m dense granule. They are thought to be autophagic granules since they are labeled with lysosomal markers (such as acid phosphatase histochemistry) [76, 77]. The cytoplasm of pyramidal neurons in the hippocampus is where they are most prevalent. They show positivity for cytoskeletal components such as neurofilament and tau in

addition to the lysosomal markers and are double membrane bound vacuoles at the EM level (e.g., cathepsin D and LAMP1). They also contain epitopes associated with apoptosis and stress granules, raising questions about their origin and importance [74, 77, 78]. These lesions can be seen under the microscope using the Bielschowsky's silver stain and hematoxylin and eosin stain, however they are not detectable using Congo red or thioflavin S fluorescent microscopy [74]. According to staging, these structures appear to build up first in the hippocampus, then in the entorhinal cortex, the temporal neocortex, the amygdala, the thalamus, the cingulate gyrus, and even the association cortices [79]. It is unclear if these vacuoles serve as a cellular defence or are more directly connected to AD pathogenesis because they have a dearth of epitopes linked to pathogenic tau [74]. Most recently, phospho-ubiquitin mitophagy markers label granulovacuolar bodies and their abundance has been shown to correlate with neurofibrillary tangle density, suggesting they may be a cellular response to damage in the neurons [80].

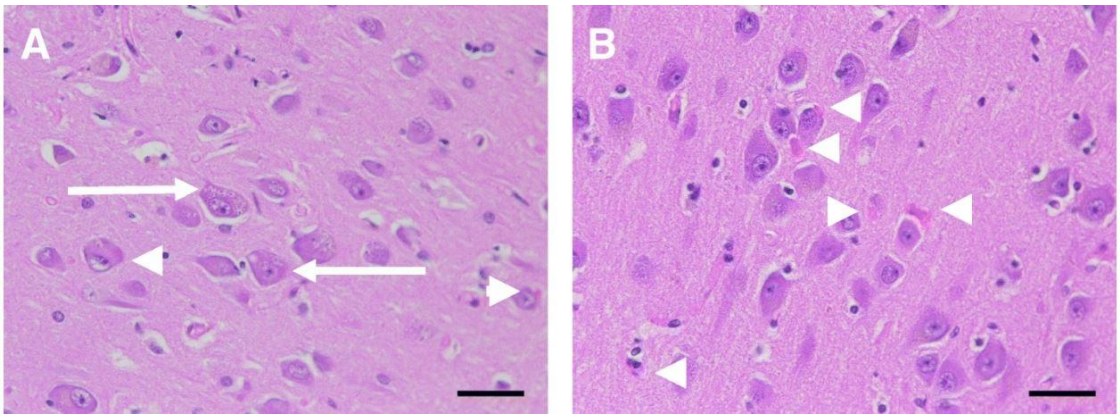

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FIGURE 6 : Granulovacuolar Degeneration and Hirano Bodies. Granulovacuolar degeneration is commonly observed in the neurons of AD.

(a) . As indicated by the arrows, these neurons contain numerous vacuoles housing a dense granule. Additionally, Hirano bodies are often observed as eosinophilic pink rods within the neurons, as shown with the arrowheads.

(b) . The scale bars are 40 μm.

Hirano Bodies

Hirano bodies, which are eosinophilic intracytoplasmic inclusion bodies observed in the presence of NFTs and GVDs but not amyloid plaques, were originally identified in Parkinson's disease complex of Guam patients [76, 81]. Hematoxylin and eosin staining reveals the rod-like inclusions in Fig. 6b, which are found in neuronal dendrites and are abundant in F-actin and actin binding proteins. In addition to AD, they have also been observed in a variety of other illnesses in middle-aged and elderly healthy individuals [81]. The CA1 area of the hippocampus is where they are most frequently seen. Compared to healthy controls, they are more prevalent and abundant in AD [82]. Their function in the pathogenesis of AD is still unknown [23]. Animal models that express mutant actin binding proteins have more recently suggested that Hirano bodies are linked to weakened synaptic responses and diminished spatial working memory [83]. To comprehend their pathophysiology and function in Alzheimer's disease, more study is required.

Inflammatory Response

Microglial cells are phagocytes that function in the brain. They keep an eye out for pathogen exposure or dying neurons, which encourages their migration to the area, activation, and occasionally antigen presentation [84, 85]. They normally play a part in synaptic monitoring and turnover, but in times of stress or degeneration (such as when protein aggregates like Aβ amyloid fibrils and tau paired helical filaments are present), they become activated and are seen around senile plaques, and their numbers rise in support of neuronal damage linked to NFTs and NT [86, 87]. Microglial activation is characterized as an innate immune response, which can be activated by multiple factors in the local environment. Receptors on microglia can bind Aβ fibrils, driving an inflammatory response similar to the M1 (proinflammatory) phenotype observed outside the central nervous system [84]. Activated ameboid microglia are frequently observed juxtaposed to amyloid deposits in plaques. This may explain the risk association of TREM2 with AD, as this microglial and astrocytic receptor is thought to mediate microglial phagocytosis [84]. The second inflammatory response seen in AD patients' brains is represented by reactive astrocytes, which are assumed to play a role in maintaining homeostasis and neuro protecting injured neurons. Normally, astrocytes serve as trophic supports for the synapses and neurons that

connect them to the vital blood supply and nutrition. They are also frequently seen near senile plaques in AD, however less frequently and farther away from the plaque epicentre than microglia. The cytokines and other substances made by pro-inflammatory M1 microglia are thought to cause them to react, and these alterations in the astrocytes are thought to be neurotoxic [88, 89].When dementia sets in later in AD, reactive astrocyte burden appears and is thought to be correlated with tau burden [90]. Additionally, oligodendrocytes and neurons have a role in controlling glia [85].

Synaptic Loss

Neuronal loss is a stronger predictor of cognitive impairments than tau burden in AD, when neurofibrillary tangle distribution is paralleled [91]. Long-lasting tangles in still neurons may linger for years as ghost tangles [23]. Perhaps more significantly, synaptic loss seems to occur before neuronal death, and these effects are likely triggered by amyloid and tau disease [92, 93]. Numerous studies using synaptic protein markers, electron microscopy, and amnestic mild cognitive impairment, which is hypothesized to precede AD, have demonstrated synapse loss in AD [92]. The correlations between cognitive decline and synaptic loss in AD appear to be stronger than those between cognitive decline and neuronal loss and tau burden [94]. It is thought that these reductions in synaptic density in the hippocampus and medial temporal lobes are responsible for cognitive loss and declines in verbal fluency early in Alzheimer's disease.

One of the initial investigations showed that axonal dysfunction affecting the presynaptic termini is probably the cause of synaptic reductions [95,96,97]. Since proteins involved in synaptic vesicle trafficking and neurotransmitter recycling, as well as structural components of the synapse, are disrupted, gene expression investigations in AD confirm these findings [92]. Clinical symptoms are connected to these pathogenic alterations' impacts on synaptic function, which appear to be directly tied to AD pathogenesis. The presence of hyperphosphorylated tau in dendritic spines and the resulting decreased synaptic transmission may complement the reduced axonal transport caused by tau dysfunction, creating a multifocal pathway for synaptic injury [98]. It is interesting to note that the residual synapses grow larger and more durable in AD, supporting the compensatory synaptic hypothesis [23].

Alzheimer's Diagnoses

Subtypes of AD

Patients who ultimately have AD at postmortem and have been diagnosed for almost 50 years have been found to exhibit atypical clinical presentations [99]. For a while, it was debatable whether there were actual variations or whether clinical heterogeneity was the result of testing at various stages of the disease's progression [100]. These are frequently considered to be clinical misdiagnoses (Table 2), and many have coexisting conditions that make clinical diagnoses more difficult. The proportion of hippocampal neurofibrillary tangles to neocortical tangles can be used to classify three primary subgroups of AD [3]. This definition includes "limbic predominate AD" and "hippocampal sparing AD," two unusual AD subtypes. Hippocampal sparring AD frequently manifests at a younger age and degenerates cognitively more quickly than usual AD.

In contrast, limbic predominate AD frequently manifests later in life and degrades cognition more gradually. It's interesting to note that 30% of individuals with hippocampal sparing may have an unusual clinical presentation. In these situations, there may be focal or asymmetrical enhanced cortical atrophy, which frequently results in clinical symptoms other than problems in episodic memory [101]. Although executive function, visuospatial, and linguistic abnormalities are all seen in AD, they are not typically the clinical manifestation [101]. Frontotemporal lobar degeneration is the most common cause of patients with primary progressive aphasias that appear as agrammatic, semantic, or logopenic variations, however hippocampal sparing AD can also manifest in this way [7, 102]. An additional unusual clinical symptom of AD that spares the hippocampi is posterior cortical atrophy (PCA). PCA can also be brought on by prion disease and cortico-basal degeneration, in addition to AD [103]. Although AD, particularly hippocampal-sparing AD, can appear in this way, frontotemporal lobar degeneration is most frequently associated with progressive executive impairment [104]. According to genetic studies of APOE4, hippocampal sparing AD and typical or limbic dominated AD are more closely related than APOE4. In instances with capillary CAA, the pathology of amyloid plaques is exacerbated. The fact that capillary CAA is associated with APOE4 and a variation of the apolipoprotein receptor LDL receptor related protein 1 (LRP-1) called C766T (rs1799986) raises the possibility that capillary CAA is possibly a subtype of AD [105, 106]. Data given in Additional file 3 and Table 3: The Mayo Clinic Brain Bank's Figure S3 shows how frequently primary AD manifests as non-amnestic symptoms. The use of antemortem amyloid and tau biomarkers, such as amyloid or tau imaging, may improve the identification of atypical AD presentations in the future [107].

TABLE 3 : Pathologic Diagnoses in 626 Patients with Clinical Diagnosis of AD. The majority of clinical AD cases as observed in the Mayo Clinic Brain Bank from 2007 to 2016 were found to have co-pathologies. Plus sign (+) in the column on pathological diagnosis of AD indicates additional pathologies beyond the primary and secondary diagnoses listed. Secondary AD indicates a primary pathological diagnosis other than Alzheimer's disease though AD changes are noted and contributing. Bold indicates significance differences from the pure AD cases (Student t-Test, $p < 0.01$)

Path Dx	Cases (n)	Age (yr)	Brain (g)	Braak	Thal
AD	108	77.3 ± 11.2	1060 ± 166	5.6 ± 0.7	4.7 ± 0.7
AD/LBD	73	79.2 ± 9.7	1017 ± 122	5.7 ± 0.5	4.9 ± 0.5
AD/LBD +	104	83.1 ± 8.3	981 ± 168	5.6 ± 0.6	4.8 ± 0.6
AD/Vas	41	84.4 ± 5.0	1007 ± 148	5.4 ± 0.8	4.6 ± 0.7
AD/Vas +	46	86.9 ± 6.6	1052 ± 135	5.2 ± 0.6	4.8 ± 0.5
AD/CAA	17	75.3 ± 14.8	1019 ± 146	5.8 ± 0.4	4.8 ± 0.4
AD/CAA +	53	80.3 ± 9.1	1045 ± 156	5.6 ± 0.5	4.7 ± 0.8
AD/HpScl	20	86.7 ± 5.8	1104 ± 143	5.5 ± 0.6	5.0 ± 0.0
AD/HpScl +	24	87.3 ± 7.5	977 ± 181	5.7 ± 0.6	5.0 ± 0.0
AD/Other	21	80.9 ± 11.0	1032 ± 135	5.5 ± 0.6	4.8 ± 0.6
AD/Other +	25	81.8 ± 10.6	950 ± 176	5.4 ± 0.7	4.6 ± 0.7
Secondary AD	15	79.5 ± 8.1	1075 ± 167	4.6 ± 0.9	4.4 ± 0.9
No AD	74	83.0 ± 7.7	1049 ± 167	2.9 ± 1.3	1.5 ± 1.7
Normal	05	87.6 ± 4.5	1140 ± 158	2.9 ± 0.2	1.4 ± 1.3

Neuropathologic Criteria

The pathologic diagnosis of AD recognizes that any amount of Alzheimer neuropathologic change is abnormal. The most current set of criteria for the neuro-pathological assessment of Alzheimer's disease termed the 2012 National Institute on Aging-Alzheimer's Association Guidelines are based on the semi-quantitative measure of Thal Aβ amyloid phase, Braak NFT stage and CERAD neuritic plaque score, and they are applicable to patients with or without dementia [69]. This contrasts to the original set of criteria produced in 1985 by the National Institute on Aging, which focused on age-related amyloid plaque density (with silver stains or thioflavin S fluorescent microscopy) without regard to type of plaque [108]. These were subsequently revised in 1991 by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which focused on neuritic plaques in the frontal, temporal and parietal cortices and included clinical presence of dementia to determine if AD was the definite, probable or possible cause of the observed symptoms [109]. Neither of these early criteria included a measure of neurofibrillary tau burden, and subsequently in 1997 the National Institute on Aging and Reagan Institute combined the CERAD neuritic plaque scoring and Braak staging to determine if clinical dementia had a high, intermediate or low probability of being caused by AD [110]. These CERAD and NIA-RI criteria also considered the effects of vascular and Lewy body disease [4]. Ultimately these criteria were revised in the 2012 NIA-AA Guidelines as it became more universally acknowledged that AD pathology can be present in the absence of clinical symptoms though there are updated clinical guidelines available for ascribing dementia to AD pathology before death [111]. The current criteria use an ABC scoring system that requires the presence of amyloid plaques and tau neurofibrillary tangles to describe the amount of AD neuro-pathological change ranging from none to low to intermediate to high amounts of change. The A score is measured by grouped Thal phase, the B by Braak stage and the C by neuritic plaque CERAD score. These guidelines include two measures of amyloid plaque burden as their independent value was not known [69]. To reach thresholds for intermediate and high Alzheimer's disease neuropathologic change, cases can have low Thal phase, but they must have a Braak stage greater than III and a CERAD score in the moderate to frequent range. Again this system retains adjustments for age and considers Lewy body disease, vascular disease and hippocampal sclerosis among other comorbidities. Additionally a practical assessment companion article was published at the same time describing the brain sections and staining techniques useful in deriving these scores [24]. Neuropathologic criteria align with revised clinical framework for considering Alzheimer type neuropathologic change in living individuals using antemortem biomarkers to assess amyloid (A), tau (T) and neuro-degeneration (N). With some combinations associated with AD preclinical stage (A+, T+, N-), symptomatic stages (A+, T+, N+) or non-AD disease processes (A-, T ±, N+) [112].

Comorbidities in Alzheimer's Disease

Cerebrovascular Pathologies

According to the vessels involved and the location of the resulting brain injury, vascular dementia is most frequently sporadic and associated with a variety of cerebrovascular diseases [113]. It covers a diverse range of illness processes that are frequently seen in tandem and become more prevalent with advancing age. The majority of AD patients have this concomitant pathology [18, 113, 114]. Approximately 16% of AD cases

in the Mayo Clinic Brain Bank also had severe cerebrovascular pathology, and individuals with mixed pathology were much older than those with pure AD. Multi-infarct dementia (MID), strategic infarct dementia, and subcortical vascular encephalopathy are the most prevalent types of vascular dementia that are seen [115], and these conditions are frequently brought on by atherosclerosis, small vessel disease (SVD), and CAA [113, 114, 116]. Larger meningocerebral arteries, internal carotid and vertebral arteries, and arteries of the circle of Willis are all shown to have atherosclerosis. These fibro-fatty intimal lesions can result in hemorrhages or infarcts of both the macroscopic and microscopic kind [113, 114, 115]. Atherosclerosis-related thrombosis and emboli are a primary cause of MID, however the condition can also be brought on by SVD or CAA [115]. Cortical and subcortical micro-infarcts can also result from SVD brought on by arteriolosclerosis and cardio-embolic illness, and these lesions are associated with cognitive abnormalities in vascular dementia [113].

Cortical infarcts, lacunar infarcts, micro-infarcts, and white matter lesions can arise from injury to the cerebral penetrating and lenticulostriate arteries, which can cause strategic infarct dementia and subcortical vascular encephalopathy (formerly known as Binswanger's disease) [113, 115]. Although capillary CAA blockage has been noted in these locations, strategic infarct dementia damage to the hippocampus or thalamus can be induced by SVD or embolic events [115]. The basal ganglia, white matter, and brainstem are frequently affected by SVD subtypes such as arteriosclerosis, lipohyalinosis, and arteriolosclerosis [116]. Leptomeningeal and intracerebral arteries may be affected by CAA, which may result in white matter lesions, micro-hemorrhages, lacunar infarcts, and cortical micro-infarcts [113]. The cerebellum, basal ganglia, and thalamus are impacted in the later stages of CAA, with white matter alterations happening last [115]. The loss of hippocampal neurons that is unrelated to epilepsy or TDP-43 illness has been linked to capillary CAA and micro-infarcts in CA1 of the hippocampus [117]. Most critically, it appears that cerebrovascular pathology interacts with AD in a synergistic manner to cause cognitive decline and dementia, and that this relationship is strongly influenced by the kind of cerebrovascular illness and the location of lesions [118]. Cerebrovascular dysfunction is projected to become more common as lifespans lengthen, and its effects on age-related cognitive decline must be taken into account.

Lewy Related Pathology

Dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) are both included under the umbrella name of lewy body dementia [119]. Pathologic deposits of α-synuclein in neuronal cell bodies, known as Lewy bodies, and neuronal cell processes (mainly axons), known as Lewy neurites, are associated with Lewy-related pathology. Lewy-related disease is susceptible to certain neuronal populations in both the central and peripheral nervous systems. Lewy related disease impacts corticolimbic areas in Lewy body dementia and is frequently linked to concomitant Alzheimer type pathologic change [120, 121]. Additionally, it has been noted that Lewy-related pathology is frequently present in AD patients' substantia nigra, and for a time, it was thought that individuals who had PD and concurrent dementia had mixed (AD-PD) pathology [18, 23]. It is now recognized that people with Lewy pathology can develop dementia that is solely brought on by the pathology; this can be seen in patients who first display Parkinsonian clinical symptoms, as in PDD, or in patients who first experience dementia, as in DLB. The relative contributions of substantia nigra tangles and Lewy bodies to this presentation are still debated in almost a quarter of AD patients [122]. Lewy bodies in AD do not exhibit the same pattern of PD-related selective vulnerability. In example, the olfactory bulb and the amygdala exhibit Lewy pathology most frequently in AD [23, 123]. It's uncertain how much clinical significance olfactory and limbic Lewy disease-related pathology will have. About 33 percent of AD cases in the Mayo Clinic Brain Bank also show Lewy-related pathology as a secondary finding, and research is being done to identify the causes of this comorbidity. It is known that tau protein and -synuclein can directly interact to promote their co-assembly, and there is evidence to suggest that A can directly alter -synuclein toxicity [124,125,126]. In addition, there are a number of potential genetic risk factors for both AD and PD, most notably APOE and MAPT [127].

TDP-43 Pathology

In addition to frontotemporal dementia's, TDP-43 protein deposition is frequently seen in AD and hippocampal sclerosis [128]. Nowadays, it is understood that TDP-43 deposits are almost always present in hippocampal sclerosis of ageing, and that occasionally arteriolosclerosis results in intracellular and neuritic TDP-43 deposits in the hippocampus during the preclinical stage and eventually hippocampal sclerosis and cerebral atrophy during the disease stage [130, 131]. Up to 10% of clinical AD cases over the age of 85 who do not have pathologically diagnosed AD may be affected by this independent disease process [130]. When TDP-43 inclusions are seen in AD, they are typically first seen in the amygdala and then the hippocampus (referred to as "limbic"), with involvement of the neocortex and subcortical areas (referred to as "diffuse") following, similar to terms used to describe the distribution of Lewy-related pathology [130, 132]. According to data from numerous studies, TDP-43 neuronal inclusions are present in between 19 and 75 percent of AD cases [132]. The majority of AD patients with TDP-43 pathology are older [130]. On antemortem brain imaging, TDP-43

distribution from limbic regions to other sections of the brain rises and is linked to medial temporal atrophy and worsening cognition [130, 132, 133]. Hippocampal-sparing AD is less likely to have TDP-43 deposits than normal AD or limbic-predominant AD [134]. TDP-43 is more common in the presence of pure AD or mixed AD/LBD compared to controls, which is similar to the higher frequency of Lewy associated pathology in AD [135]. This is a rapidly expanding field of research, and more work will be needed to elucidate how TDP-43 pathology is related mechanistically to AD pathology and their downstream effects.

Argyrophilic Grain Pathology

Tau can be deposited as either 3R tau or 4R tau in many primary tauopathies, but it is typically deposited as PHF comprised of 3R and 4R tau in Alzheimer's disease. Argyrophilic grain disease (AGD) is a 4R-tauopathy [136] that causes inflated neurons, ramified astrocytes, and oligodendroglial inclusions (also known as "coiled bodies") in the amygdala, hippocampus, and medial temporal lobe. AGD has been observed in up to 25% of AD cases and is linked to amnestic cognitive impairment. Its frequency rises with age. These findings are supported by data from the Mayo Clinic Brain Bank [139]. Antibodies that are specific for 4R tau that easily identify grains from the tangles and threads of AD can be used to confirm a pathologic diagnosis of argyrophilic grain disease. In addition to being more frequently seen in people with Alzheimer's disease than in the general population, argyrophilic grain disease also decreases the pathological threshold for the onset of clinical dementia [140].

Age Related Tau Pathologies

Primary age-related tauopathy (PART) and aging-related tau astrogliopathy (ARTAG) are two distinct tau pathologies that are frequently seen in people over the age of 80. PART may be responsible for some of the clinical AD cases in the elderly that are incorrectly identified [130, 141, 142]. The 3R and 4R isoforms of the neurofibrillary pathology in PART are comparable to those in AD. While PART is unique from AD in that it lacks amyloid plaques and has a separate morbidity and age range, it has lesions in the hippocampus and surrounding regions that are comparable to those seen in Braak I–IV [130, 142]. When AD prevalence is stable or decreasing in the 1980s and 1990s, the frequency of PART rises [130]. Pretangles in PART may develop into NFTs, then extracellular ghost tangles, following a similar process to that seen in AD. When they occur frequently, the latter are linked to memory difficulties seen in senior people [130, 142]. It is still difficult to tell PART from AD [130]. Astrocytic tau pathology, such as that seen in primary tauopathies like PSP, CBD, and GGT, is represented by ARTAG. It is linked to 4R tau deposits in grey matter that are found in subpial or perivascular thorn-shaped astrocytes or granular fuzzy astrocytes [130]. Although it is advised that the site, region, and severity of ARTAG be noted, its connection to neurological symptoms is not fully understood [130].

Preclinical Alzheimer's Disease

At the time of autopsy, Alzheimer's pathology can be identified in people who were cognitively normal, and this preclinical stage can also be seen in patients who had mild cognitive impairment but did not fulfil the clinical criteria for AD [4, 23]. It is now unknown whether clinically normal AD pathology patients who had lived longer would have shown clinical signs [55, 143]. To improve early and accurate clinical diagnoses for potential therapeutic intervention, recommendations for defining the preclinical stages of AD are made. As a result, these recommendations call for acknowledging amyloid and tau pathology as well as synaptic loss as substrates for the clinical manifestations of AD [144]. Despite a reported risk of 10-15% for developing dementia, people with amnestic moderate cognitive impairment do not always have AD at autopsy, and occasionally they do not have any discernible pathology [145, 146]. In fact, the clinical criteria for AD concentrate special attention on patients who have positive amyloid and tau biomarkers, while also taking care to document dementia and its course and rule out other possible disorders [111]. The majority of this work is still in the research stage right now. Most working clinicians do not have access to amyloid and tau biomarkers. Molecular imaging is not currently covered by insurance, and spinal fluid evaluations are not typical procedures. Even with the greatest imaging, neuro-pathological diagnoses will continue to be the norm for identifying comorbidities and attributing clinical symptoms to their underlying causes. Amyloid plaques and tau neurofibrillary tangles are what define AD.

II. CONCLUSION

A growing medical catastrophe, Alzheimer's disease has a devastating personal and financial impact on those who have it and their families. Lack of standard diagnostic technologies that can identify patients early enough in their course for therapy exacerbates the issue. The absence of efficient therapy alternatives after the disease process has been identified is also a cause for concern. Future studies are required to identify AD's underlying causes and the clinical presentation's wide range. In order to create the most efficient treatments, there needs to be a greater understanding of the comorbidities that influence clinical results. Future treatments

will be multimodal, focusing on the disease through various channels to stop both the basic disease pathogenesis and extra unwanted cellular responses. This is because ageing brains are associated with multiple proteinopathies. The development of precise and sensitive diagnostic tools must progress concurrently with therapeutic methods in order for them to be effective. The costs to the millions of individuals impacted by this condition are significant, as are these difficulties.

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CONFLICT OF INTERESTS

The Author declares there is no any Conflict of Interests.