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Current Concepts in Alzheimer's Disease: A Multidisciplinary Review

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This comprehensive, pedagogically-oriented review is aimed at a heterogeneous audience representative of the allied disciplines involved in research and patient care. After a foreword on epidemiology, genetics, and risk factors, the amyloid cascade model is introduced and the main neuropathological hallmarks are discussed. The progression of memory, language, visual processing, executive, attentional, and praxis deficits, and of behavioral symptoms is presented. After a summary on neuropsychological assessment, emerging biomarkers from cerebrospinal fluid assays, magnetic resonance imaging, nuclear medicine, and electrophysiology are discussed. Existing treatments are briefly reviewed, followed by an introduction to emerging disease-modifying therapies such as secretase modulators, inhibitors of Abeta aggregation, immunotherapy, inhibitors of tau protein phosphorylation, and delivery of nerve growth factor.

Keywords: Alzheimer's disease; neuropathology; neuropsychological testing; neuroimaging; pharmacotherapy

Introduction

When a case of Alzheimer's disease (AD) was first reported in 1907, life expectancy was much shorter than today. A diagnosis of AD was relatively uncommon and limited to demented patients younger than 65 years, and the future devastating impact of the disease remained unrecognized until, in a 1976 editorial, Katzman first argued that senile dementia and AD formed a continuum.[1,2]

Today, the disability weight of AD on individuals older than 60 years of age is larger than that of stroke, musculoskeletal disorders, cardiovascular disease, and cancer.[3] It is estimated that 25 to 30 million people worldwide currently suffer from AD and, as shown in Figure 1, according to current estimates the number of cases will approximately triplicate by 2040.[4] After 65 years of age, the prevalence of AD doubles approximately every 5 years.[4] In addition to the impact on the lives of patients, AD places a substantial psychological and economical burden on caregivers. For example, in the UK caring for institutionalized AD patients (about 50% of the total) costs about 0.6% of the gross domestic product, while in the USA the annual cost of care for patients living with their families was estimated to be about 0.3% of the gross domestic product in 1998.[5,6] As life expectancy steadily increases, AD is set to become the greatest health care challenge of modern history.

Alzheimer's disease exists in both familial and sporadic forms. Familial forms are caused by mutations in single genes that are inherited in an autosomal-dominant fashion, and account for about 5% of cases. Sporadic forms have a multifactorial etiology, in which some genetic polymorphisms are known to act as predisposing factors.[7]

Three genes are currently known to be implicated in the familial forms of AD. Mutations in the gene encoding for the amyloid precursor protein (APP, see next section) were the first to be identified in 1991 and, to date, 18 AD-related mutations are known.[8,9] The majority of familial cases are, however, caused by mutations in the genes encoding for

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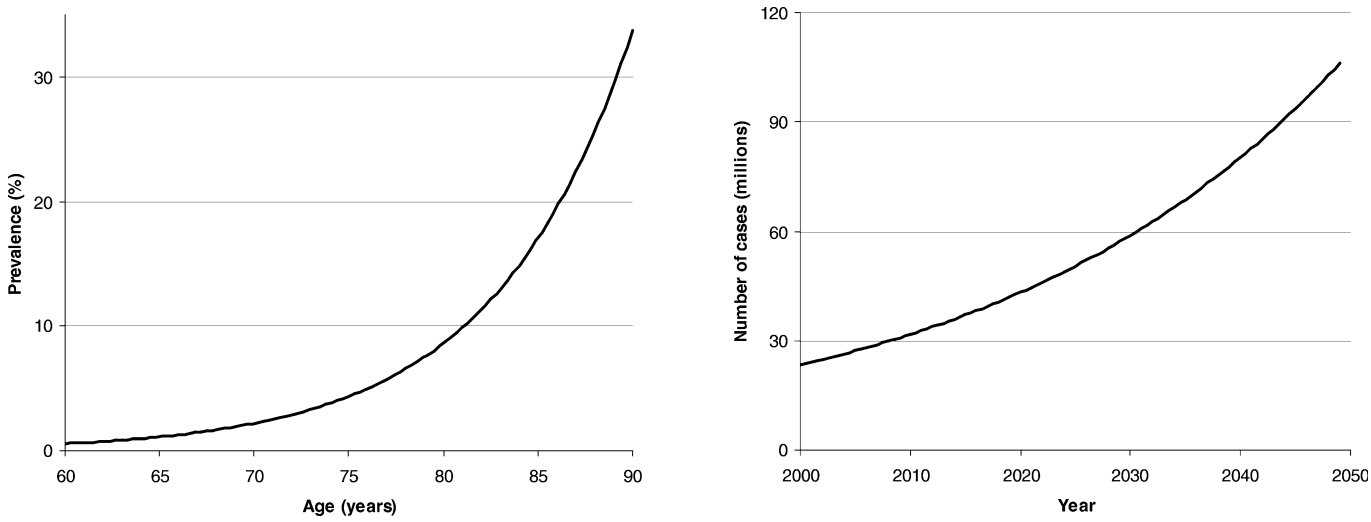

Figure 1. Prevalence of Alzheimer's disease (AD) as a function of age (left) and total number of cases as a function of calendar year (right). Based on data from the Delphi consensus study by Ferri et al.[4]

presenilin-1 and presenilin-2 (PSEN1 and PSEN2), which are part of the γ-secretase complex (see next section); at the time of writing, 152 pathogenic mutations are known.[7,9]

Several genes are known to play a role in the pathogenesis of sporadic AD. The most consistent findings have thus far been obtained for the gene encoding for apolipoprotein E (APOE); although the exact mechanism of action remains to be determined, there is evidence that it may modulate γ-secretase activity.[7,10] Patients with AD are more likely to carry the ε4 allele than the general population, and a proportional relationship between gene dose and risk and age of onset has been found.[11] Conversely, the ε2 allele may confer a relative protection.[12] There is also some evidence indicating that variants of the gene encoding for the insulin-degrading enzyme (IDE), which is active in the degradation of amyloid-β (Abeta), may predispose individuals to the disease.[13] Another gene known to be implicated in AD is ubiquilin-1 (UBQLN1), which affects intracellular APP trafficking.[14] Variants of the *SORL1* gene, which encodes for a neural receptor of APOE, have also been associated with AD.[15] Furthermore, links between the pathogenesis of AD and variants of the α-2 macroglobulin, interleukin 1, interleukin 6, and tumor necrosis factor α genes have been established.[7] A polymorphism of CALHM1, a gene encoding for a transmembrane protein influencing calcium levels and Abeta production, was recently found to increase the susceptibility to late-onset AD.[16] A comprehensive review of the genetics of AD can be found in the article by Serretti et al.[7]

Old age and presence of disease-predisposing genetic polymorphisms are the most important risk factors. Some studies pointed to a link with cerebrovascular pathology, but it remains unclear whether there is a true causal relationship, for example with microvascular abnormalities leading to impaired clearance of APP and soluble Abeta, or whether the vascular lesion load simply adds to that of AD making diagnosis more likely.[17] Notably, several studies have demonstrated that small white matter infarcts, while lacking acute symptoms, are a significant predictor of cognitive decline in the elderly.[18,19] Another risk factor is traumatic brain injury which, despite discordant findings, is increasingly believed to activate neurodegenerative processes leading to the accumulation of Abeta and tau pathology (see next section); the exact mechanism remains unknown.[20] Several studies converge in indicating that a history of depression can predispose to the disease; of note, even though depression may also represent a prodromal manifestation of AD, the risk of developing AD has been reported to be higher in individuals who develop depressive symptoms early in life, supporting the hypothesis that depression is an independent risk factor.[21,22] Because of the lack of a significant cognitive reserve, which can delay the cognitive expression of pathology in the early stages of the disease, individuals with poor education and low mental ability have a higher probability of being diagnosed with AD.[23]

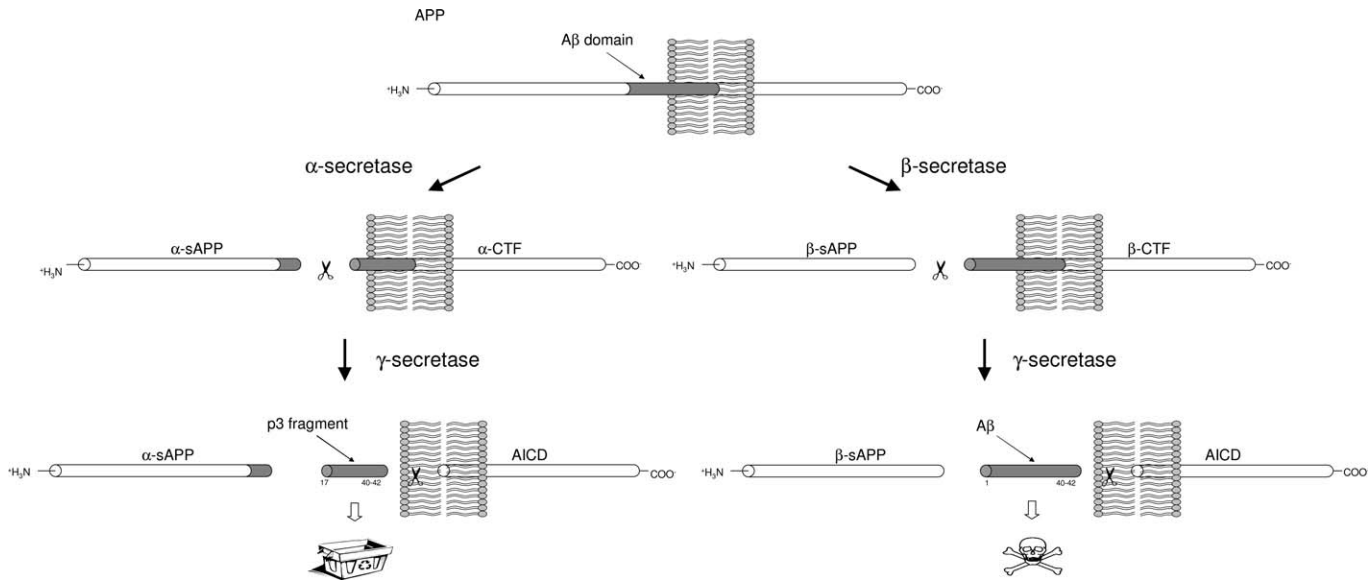

Figure 2. Metabolism of the amyloid precursor protein (APP). Cleavage of the APP takes place through competing α-secretase and β-secretase, which release soluble extracellular fragments (α-sAPP and β-sAPP). Cleavage of the APP by α-secretase takes place in the Abeta region, thereby preventing release of the full-length Abeta; cleavage of the resulting C-terminus fragment (α-CTF) by γ-secretase releases a harmless P3 fragment. By contrast, cleavage of the APP by β-secretase leaves the Abeta region attached to the C-terminus fragment (β-CTF); subsequent cleavage by γ-secretase releases various isoforms of Abeta.

Pathogenesis and Neuropathology

The Amyloid Cascade Model

The core hypothesis of the amyloid cascade model, which forms the backbone of the current understanding of the pathogenesis of AD, is that accumulation of Abeta is an early event leading to neurodegeneration.[24]

The APP has the characteristic of a cell surface receptor and is expressed in many tissues, in particular in synapses, as a part of normal metabolism. Although its primary function remains unclear, the APP is believed to be implicated in synaptic formation and repair, signaling, and cell adhesion.[25] Several isoforms ranging in length between 365 and 770 amino acids exist, some of which appear more closely associated with the pathogenesis of AD than others.[26]

As depicted in Figure 2, the Abeta region of the APP spans the cell membrane. The APP is cleaved by α-secretase and β-secretase, both of which release a soluble extracellular fragment (α-sAPP and β-sAPP). Cleavage by β-secretase leaves the Abeta region attached to the C-terminus fragment (β-CTF), while α-secretase cleavage takes place within the Abeta region, thereby preventing release of the full-length Abeta polypeptide. The α-CTF and β-CTF are subsequently cleaved by γ-secretase in the transmembrane region releasing, respectively, either a harmless p3 fragment or the Abeta polypeptide.[25]

Both pathways are active in normal metabolism. Several ADAM proteins, a class of peptidases which shed the extracellular portion of transmembrane proteins, are known to have α-secretase activity.[27] The physiological roles of the Abeta converting enzyme 1 (BACE1) and of its homologue BACE2, both of which have β-secretase activity, are less clear, but several non-APP substrates have been identified and BACE1-knockout mice display behavioral and metabolic abnormalities.[28,29] Notably, several recent studies have demonstrated decreased α-secretase activity and increased β-secretase activity in sporadic AD.[29,30] In addition to its role in APP processing, the γ-secretase complex is important in the cleavage of Notch, a widely expressed transmembrane protein involved in cell communication.[31]

Amyloid precursor protein cleavage through β-secretase and γ-secretase can produce several isoforms of Abeta, of which the 40 and 42 amino-acid forms are the most common ones.[25] Abeta(40) is considerably less prone to oligomerization (ie, the process of aggregating into oligomers from which larger, insoluble fibrils are formed) than Abeta(42) and is regarded as less neurotoxic.[32] The

Abeta(42)/Abeta(40) ratio can be influenced by several factors, including substrate concentration as well as PSEN1 and PSEN2 mutations.[33,34] Several enzymes are active in the catabolism of Abeta, including the insulin-degrading enzyme (IDE), neprilsyn and the endothelin-converting enzyme, and, as discussed in the previous section, some variants of IDE appear to predispose to the disease.[13,35]

In contrast with the familial forms, what determines Abeta accumulation in sporadic AD remains largely unknown. Hypothesized mechanisms include altered expression of APP, abnormal deactivation of α-secretase and activation of β-secretase, abnormal modulation of γ-secretase leading to increased production of Abeta(42), reduced activity of the Abeta-degrading enzymes, and reduced clearance of APP and soluble Abeta.[24,25]

Crucially, the exact mechanism of Abeta toxicity remains elusive. Once released, Abeta undergoes complex conformational changes, transitioning from small soluble fragments and oligomers into large fibrils, which in turn form plaques. A recent study on transgenic mice confirmed the toxicity of Abeta plaques, which cause microglial activation within few days of formation followed by neuritic degeneration.[36] Furthermore, in recent years evidence has accumulated pointing to a significant neurotoxicity of Abeta oligomers, which have much larger surface-to-volume ratio and diffusivity.[37]

Neurofibrillary tangles, the other neuropathological hallmark of AD, are principally composed of abnormally phosphorylated tau protein, a normal axonal protein that binds to microtubules and that has an essential role in their assembly and stability. The exact link between Abeta and tau protein pathology remains unclear. Broadly, it is believed that altered ionic homeostasis and oxidative stress following Abeta accumulation alter the balance between the phosphatases and kinases which regulate the level of phosphorylation of tau protein, leading to its hyperphosphorylation, separation from microtubules, abnormal accumulation, and polymerization with tangle formation, ultimately causing synaptic dysfunction and axonal loss.[38,39]

Support for the amyloid cascade model comes from observations of extensive Abeta deposition in the AD brain, from the fact that the genes implicated in familial forms are all related to APP processing, and from evidences of dysregulated APP metabolism in sporadic AD. However, the model has not yet been formally tested and important issues remain open. For instance, the existence of a direct causal relationship between Abeta deposition and the formation of neurofibrillary tangles is put into question by the fact that, in the early phases of the disease, large amounts of neurofibrillary tangles appear in medial temporal structures where the density of amyloid plaques is low.[40] Furthermore, the correlation between the density of amyloid plaques and clinical dementia ratings is weak.[41] Another issue is that single-transgenic mouse models, despite massive deposition of Abeta, do not show substantial accumulation of neurofibrillary tangles and neuronal degeneration.[42]

Neuropathology

Progressive cortical atrophy is the main gross anatomical correlate of AD and is normally more marked in the frontal, parietal, and temporal lobes with relative sparing of occipital, and primary motor and sensory regions. Atrophy of the hippocampus is prominent and can extend to the amygdala. The ventricles, particularly the temporal horns, are frequently enlarged. Notably, none of these features are specific to AD.[43]

Alzheimer's disease is unique in the fact that it is characterized by the misfolding of unrelated proteins, Abeta and tau protein, causing distinct histopathologic changes that converge in the paradigmatic lesion of AD, the senile plaque, which is composed of Abeta deposits surrounded by degenerating neurites accumulating tau protein.

At the ultrastructural level, β-amyloid takes the form of β-sheet rich, 8- to 10-nm long straight fibrils. Senile plaques have a diameter ranging between 10 and 160 μm and appear as radiating bundles of amyloid, with or without a dense central core (Figure 3A). They frequently include neuronal (ie, neurites and synaptic terminals) and glial (ie, reactive astrocytes and activated microglia) cellular elements.[43,44] Diffuse plaques, commonly referred to as "preamyloid deposits," are much less dense and consist of nonfibrillary forms of Abeta (Figure 3B).[45] They are only visible with immunohistochemical techniques and are hypothesized to represent an early stage in the formation of senile plaques. Abeta deposits are also found in the vessel walls, in the form of congophilic amyloid angiopathy (Figure 3C).[43,44]

Co-occurring with extracellular Abeta accumulation, the intracellular build-up of twisted filaments, mainly consisting of abnormally phosphorylated tau protein, takes place within the perykaria and neurites of selected neuronal populations. Their accumulation leads to the formation of neurofibrillary tangles, which take a flame-shaped appearance in pyramidal neurons and a globose shape in basket and stellate

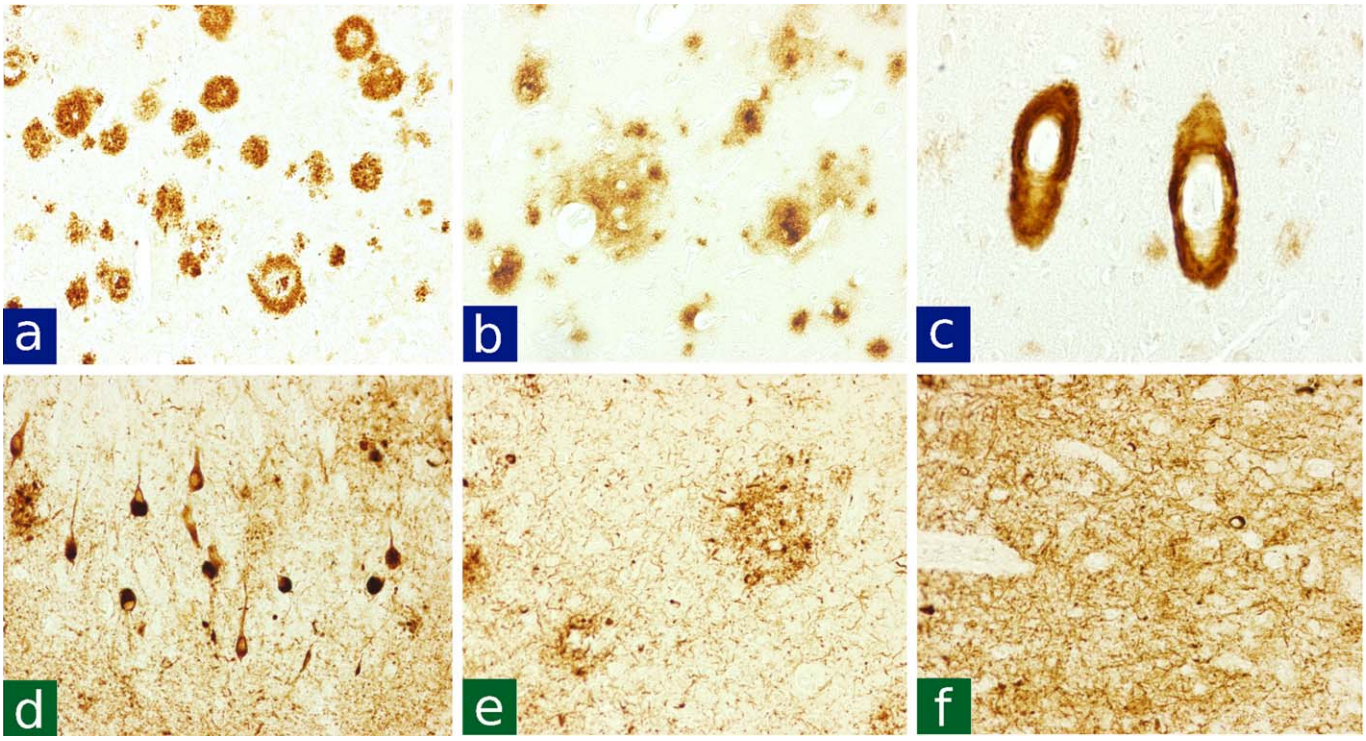

Figure 3. Neuropathological lesions as revealed by immunohistochemistry (immunoreactivity corresponds to brown reaction product, magnification ×400). Immunohistochemistry with antibodies to Abeta: senile plaques (A), preamyloid deposits (B), and amyloid angiopathy (C). Immunohistochemistry for phosphorylated tau (AT8): neurofibrillary tangles (D), clustering of dystrophic neuritic profiles in senile plaques (E), and neuropil threads (F).

cells (Figure 3D and E). Hyperphosphorylated tau protein tends to unbind from the microtubules and to accumulate ectopically in perykaria and dendrites, leading to neuronal degeneration and to the appearance of randomly-oriented neurites dispersed in the neuropil, commonly referred to as "neuropil threads" (Figure 3F).[43,44,46]

Abeta deposits initially accumulate in basal regions of the cortex, subsequently spreading with a gradual pattern to most associative neocortical areas; the hippocampal formation is relatively spared, and sensory and motor areas are significantly affected only in end-stage AD.[40] Although in generally smaller amounts, Abeta deposits can also be found in the brains of non-demented individuals.[47,48] Some studies have found a correlation between plaque counts and the clinical severity of dementia, but according to others, plaque density alone does not account for the degree of cognitive impairment.[41,49]

The accumulation of neurofibrillary pathology follows a hierarchical pattern, in which alterations are initially confined to the entorhinal cortex and hippocampus (Braak and Braak stages I-II) and extend to the neocortex only in late stages of the disease (stages V-VI).[40] The basal nucleus of Meynert is affected relatively early, and the temporal progression of symptoms follows the distribution of neurofibrillary pathology more closely than that of amyloid plaques.[40,41,50] Neurofibrillary tangles can also be found in non-demented patients, confined to the medial temporal structures; moreover, they are not specific to AD as they are also present in other sporadic and familial neurodegenerative disorders such as progressive supra-nuclear palsy and cortico-basal degeneration.[51]

Symptoms

Pathological Correlates

As confirmed by clinico-pathological studies, the cognitive deficits observed in AD mainly follow synaptic loss and axonal dysfunction, occurring initially in the entorhinal cortex and hippocampus and subsequently in associative neocortical regions.[41,52] The consequences of diffuse pathology are exacerbated by the loss of up to 95% of the cholinergic innervation to the cortex, caused by extensive degeneration of the

cholinergic neurons in the basal nucleus of Meynert and in the medial septal nucleus.[53,54] The availability of acetylcholine is further reduced due to the declining activity of choline acetyltransferase, the enzyme responsible for its synthesis.[55] Storey et al provide a comprehensive review of the cognitive symptoms of AD.[56]

Memory

Slow, progressive impairment of episodic memory typically accompanies AD from the preclinical phase.[57] During its early stages, AD may be designated as amnesic mild cognitive impairment (MCI), an etiologically heterogeneous entity representing the overlap between normal aging and the early phases of AD and other forms of dementia. Amnesic MCI is characterized by memory impairments that are beyond the level expected for the age but which do not significantly interfere with daily living activities, high level of insight, and absence of other symptoms of dementia.[58,59]

Initially, subtle deficits of verbal and nonverbal anterograde episodic memory appear in very mild AD, paralleled by temporally-graded deficits of retrograde episodic memory with relative preservation of memories of older events.[60,61] This temporal gradient reflects the fact that, while the entorhinal cortex and the hippocampus are essential for the acquisition and consolidation of new memories, long-term memories are consolidated into a diffuse multifocal neocortical representation.[62,63] Interestingly, in semantic dementia, early degeneration of the neocortex leads to the reverse temporal gradient.[64]

The disruption of recent memory consolidation in mild AD results in the emergence of failure to benefit from repeated presentation of items to be learned.[65] Analysis of recalled items reveals additional deficits including the loss of the primacy effect (enhanced recall of the first items of a list) with relative sparing or even apparent boosting of the recency effect (enhanced recall of the last items of a list), the loss of the isolation effect (enhanced recall of salient items), and the loss of emotional memory enhancement.[66-69] Furthermore, the advantage of delayed recognition over delayed recall is reduced or lost, in line with the hypothesis of encoding-stage dysfunction.[70]

Progressive disintegration of semantic memory becomes evident in mild AD, paralleling damage and reduced cholinergic innervation to the temporal neocortex.[57,71] In clinical settings, this is observed in tests of word list generation by semantic category as early "drying-up," with reduced semantic clustering and switching as well as increased perseverative and intrusion errors; by contrast, word list generation by letter, albeit below norm due to incipient frontal dysfunction, is relatively spared.[72,73] Semantic deficits are also revealed as difficulties in confrontation-naming and in generating verbal definitions.[74] Access deficits are reflected in conversation as empty speech, characterized by circumlocutions, paraphasia, and intracategory and supracategory errors.

In contrast with the progressive deterioration of the declarative memory systems, portions of implicit memory remain relatively preserved even in severe AD. For example, patients with moderate-to-severe AD can learn to perform a fine motor skill and retain it for at least a month, thanks to the sparing of neostriatal and cerebellar networks.[75] Furthermore, despite the fact that conceptual priming (the implicit memory advantage gained from prior exposure to semantically related material without conscious recollection) is impaired, perceptual priming (the implicit memory advantage gained from prior exposure to perceptual features of an object), is relatively preserved, as demonstrated using short fragments of text and pictures.[76,77]

Language

The language deficits are initially related mainly to the dissolution of semantic memory and to impairment of the executive component of verbal fluency, but, as the disease progresses, the grammatical structure of spontaneous speech becomes simpler, repetition deteriorates, language becomes paraphasic and eventually unintelligible due to articulatory and phonological deficits.[78-81] The structure of verbal and written language normally decline in parallel with progressive loss of function words and increasing use of passe-partout words and, although reading aloud is preserved in some advanced cases, comprehension of complex sentences is visibly impaired early in moderate AD.[80,82] In written language, the prevalence of spelling errors gradually increases, initially due to phonological errors, and problems with letter formation appear in moderate AD.[83,84] In severe AD, purposeful verbal communication is completely lost and mutism and echolalia ensue.

Visual Processing

Deficits of visuospatial perception can also be detected in the early stages of the disease, manifesting as drawing, construction and orientation impairments.[85-87]

In parallel, associative visual agnosia emerges, mainly as a result of the loss of semantic and lexical knowledge.[86-88] Although apperceptive visual agnosia is generally related to severe AD and to posterior variants of AD, deficits of perceptual organization have also been detected in very mild AD.[89-90]

Executive Function and Attention

Several studies have demonstrated that dysexecutive symptoms accompany AD already in the early stages of the disease, emerging in parallel with episodic memory dysfunction and generally before the onset of significant language and visuospatial impairments.[91-94] It has been claimed that many of the early problems experienced by patients with AD in performing everyday activities are determined by executive dysfunction.[92,95] Although it remains debatable whether all executive functions are affected in parallel or whether there are dissociations, there is general consensus regarding the early onset of impairments in inhibition, task-switching, and concurrent manipulation of information.[91-94,96] Additionally, some studies detected early deficits in concept formation and reasoning in very mild AD.[94]

Although engagement of attention appears to be relatively spared, difficulties in shifting attention from a task or object to another appear early in the course of the disease, reflecting dysfunctional supervisory control and response inhibition.[92,97,98] Attention shifting problems have been demonstrated in tests involving the identification of overlapping line drawings and in tests requiring selective focus on local or global visual features, and specific abnormalities in the response to visual cues have also been reported.[92,99-101] Left hemispatial neglect can also occur.[102] The ability to sustain attention has been less thoroughly studied, but a recent report highlighted an increased rate of decrement over time in patients with mild AD with respect to controls.[92,103]

Praxis

Apraxic symptoms occur in about a third of patients with mild AD and in virtually all patients with severe AD.[104] There is good agreement among studies in demonstrating impairment of transitive limb movements, which require the translation of movement onto an object (eg, hammering a nail or brushing one's teeth), but findings are discordant as to whether ideomotor apraxia (ie, deficits in transcoding the concept of a motor sequence into corresponding actions) or ideational apraxia (ie, impaired knowledge of actions) appears first in the progression of the disease.[104-107] Although ideomotor apraxia occurs independently of the ability to acquire new motor skills, ideational apraxia appears to be closely linked with semantic memory deficits.[107,108] Paralleling limb apraxia, bucco-facial ideomotor apraxia is found in approximately a third of early AD patients.[109]

Constructional apraxia (ie, the inability to combine given elements into a meaningful whole) also occurs in AD, and its presence in early stage predicts rapid cognitive decline.[110,111] The "closing-in" phenomenon, that is the tendency to copy a figure very closely or even within the given model, is a subtype of constructional apraxia that appears to have good specificity for AD with respect to other dementias.[112]

Behavioral Symptoms

Clinically relevant behavioral symptoms occur in about 90% of patients at some point during the course of the disease with 20% to 50% of patients diagnosed with comorbid depression, and, according to some authors, their onset may precede diagnosis by up to 3 years.[113-116] These symptoms negatively affect the cognitive and functional status and substantially increase caregiver burden, significantly contributing to the risk of institutionalization.[117]

In mild AD, agitation, anxiety, irritability, and apathy are the most common symptoms followed by disinhibition in moderate AD, while in severe AD apathy, social isolation and withdrawal are the most common symptoms followed by agitation, aggression, increased confusion, wandering, and aberrant motor behavior and vocalization.[114] Delusions, hallucinations, dysphoria, and euphoria also occur, but their overall prevalence is lower and possibly not significantly different between mild and severe AD.[114,118] Alzheimer's disease is frequently accompanied by sleep disturbances, which may contribute considerably to memory deficits and cognitive dysfunction.[119] Affective disturbances such as pathological attachment to objects and aberrant sexual behavior have also been reported in moderate-to-severe AD.[120,121]

The etiology of the behavioral symptoms of AD remains unclear, but their appearance is thought to be related to concurrent degeneration and loss of cholinergic innervation of the frontal, limbic, and paralimbic cortices, as well as to hippocampal and amygdalar involvement and to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and of the noradrenergic and serotonergic systems.[122-124]

There is strong evidence of altered density of serotonin receptors in frontal and temporal cortical regions, offering a possible explanation for the high incidence of depression in patients with AD.[125,126] Two recent single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies (see next section) highlighted reduced perfusion and glucose metabolism in the frontal lobe in patients with AD having comorbid depression with respect to AD patients without depressive symptoms, confirming that frontal dysfunction, known to be associated with primary and secondary depressive syndromes, also underlies the depressive symptoms of AD.[127,128] Interestingly, the plasma Abeta(42)/Abeta(40) ratio has been reported to be altered in elderly individuals with depressive symptoms with respect to those without depression, leading to the hypothesis that a distinct subtype of depression, referred to as "amyloid-depression," could be a prodromal manifestation of AD; this hypothesis, however, does not find support in a large study which concluded that the prevalence of depressive symptoms is not higher during the prodromal phase of AD.[129,130]

Cognitive anosognosia (ie, unawareness of the cognitive symptoms) is common in AD. Notably, it has been shown that while MCI patients tend to overestimate the severity of their symptoms, patients with AD tend to underestimate them even in mild stage.[131] Cognitive anosognosia is progressive, and the level of insight correlates inversely with disease severity.[132,133] Of note, dissociation between awareness of the cognitive and of the behavioral symptoms has been reported.[134]

Diagnosis

Clinical Diagnosis

At the time of writing, a diagnosis of AD is established, in the vast majority of cases, by means of clinical examination and neuropsychological assessment. The diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) are frequently taken as main reference, but other sets of diagnostic criteria such as those set forth in the *International Classification of Diseases* (10th Revision; *ICD-10*), and in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; *DSM-IV-TR*) are also in widespread use.[135-137] The common prerequisite for a diagnosis of AD to be established is the presence of clinically significant cognitive impairment with gradual onset and without secondary causes of dementia.

The initial clinical interview and anamnesis provide information on the pattern of onset, on the duration of symptoms, and on their severity, using subjective patient and relative reports. Secondary causes of dementia, such as vascular dementia, intracranial mass, normal-pressure hydrocephalus and neuropsychiatric disorders need to be excluded. To determine the severity of cognitive impairment, the Mini-Mental State Examination (MMSE) and the more extensive Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) and neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) are frequently employed.[138-140] In addition, functional status is assessed using tools such as the Activities of Daily Living (ADL) scale, and the presence, severity and impact of neuropsychiatric symptoms and associated caregiver distress can be evaluated using the Neuropsychiatric Inventory (NPI).[141,142]

Traditional depression scales such as the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HDRS) and the Geriatric Depression Scale (GDS) are frequently used to detect comorbid depression in AD. However, there is substantial research indicating that depression co-occurring in AD is qualitatively different from other depressive disorders and assessment of depression is particularly problematic. Symptom-based assessment is associated with overestimation, structured interviews tend to underestimate prevalence and severity and subjective reports have to be interpreted carefully to take into account potential denial, apathy, impaired verbal expression, alexithymia, and confusion.[143] The Cornell Scale for Depression in Dementia (CSDD) has been specifically designed for use in AD and uses information from interviews with both the patient and a caregiver, providing higher sensitivity and reliability.[144,145] In an attempt to improve differentiation between AD-related depression and other depressive disorders, provisional diagnostic criteria (NIMH-dAD) have been developed; a recent comparison study revealed that these criteria identify a higher proportion of patients with AD as depressed in comparison with the GDS and the CSDD.[143,146]

Global scales such as the Global Deterioration Scale (GDS) and the Clinical Dementia Rating (CDR) provide an overall quantification of the severity of dementia symptoms and include cognitive, functional, as well as neuropsychiatric elements.[147,148]

Detailed neuropsychological assessment can support diagnosis by revealing the pattern of cognitive deficits typical of the AD neuropsychological profile, informing differential diagnosis between the dementias and other age-related cognitive disorders. A measure of the premorbid IQ and current cognitive status can be obtained using, respectively, the National Adult Reading Test (NART) and the MMSE to define the extent of global cognitive decline compared to intellect.[149] Memory impairments including rapid rate of forgetting, poor delayed recall, and poor recognition can be detected using the Hopkins Verbal Learning Test (HVLT), the Rey Auditory Verbal Learning Test (RALVT), or the California Verbal Learning Test (CVLT), that provide measures of learning, immediate and delayed recall, recognition, and sensitivity to interference.[150-152] Paired associate learning tests highlight acquisition impairments specific to AD and are useful in differentiating between semantic dementia and AD.[153] The Clock Drawing Test and the Rey-Osterrieth Complex Figure Test are frequently administered, alongside other tests that reveal spatial memory, attentional, and apraxic deficits.[104,154,155] Working memory can be tested using letter number sequencing, forward and backward digit span that form part of the Weschler Memory Scale (Third Edition; WMS-III), and the ability to remember complex material can be assessed using the Logical Memory assessments, that are also part of the WMS-III.[156] To assess everyday memory and executive functioning problems with greater ecological validity, the Rivermead Behavioral Memory Test (RBMT), the Multiple Errands test and the Behavioral Assessment of the Dysexecutive Syndrome (BADS) can be used effectively.[157,158] In clinical settings, executive functioning is frequently evaluated with traditional tasks that are sensitive to deficits in cognitive flexibility, switching ability, and cognitive inhibition, which manifest as perseverative and intrusion errors on verbal fluency tasks, as well as on performance in the Stroop task, in the Wisconsin Card Sort, and in the Trail Making task.[159-162] The recently developed Delis-Kaplan Executive Function Battery (DKEFS) combines a range of traditional and everyday measures, refined to improve sensitivity to early inhibitory, switching and semantic impairments associated with AD.[163] Semantic category fluency tests, comprehension tests such as the token test, repetition tests, confrontation-naming tests such as the Boston Naming Test, and the Pyramids and Palm Trees test are also in use.[72,164-166]

Although the agreement between clinical diagnosis and the neuropathological gold standard is reportedly around 80%, this figure is positively biased with respect to first diagnosis, given that it takes into account follow-up.[167] As disease-modifying therapies become a more concrete perspective, the need for improved accuracy in early diagnosis will become compelling, motivating the use of techniques more expensive than neuropsychological assessment, such as nuclear medicine, in clinical everyday practice. This trend is reflected in recent proposals for revised diagnostic criteria, which include laboratory tests as well as structural and functional neuroimaging as sources of supportive evidence to corroborate the clinical diagnosis.[168]

Laboratory Biomarkers

Approximately 60% of patients with AD have at least one APOE ε4 allele, and a study on 2200 patients indicated that addition of APOE genotyping to clinical diagnosis, while reducing its sensitivity, can improve it specificity from about 55% to more than 80%.[169] At the time of writing, APOE genotyping is not frequently used outside research settings on demented patients and never used on asymptomatic individuals, because of its limited predictive power, psychosocial implications, and undetermined role in changing patient management with currently available therapies.[170]

Although the diagnostic accuracy of urinary and plasma biomarkers has thus far proven disappointing, more consistent results have been obtained with enzyme-linked immunosorbent assaying of cerebrospinal fluid (CSF).[171] The CSF concentration of Abeta(42) is reduced in patients with AD with respect to controls, probably as a result of increased sequestration into insoluble deposits.[172,173] Although it can provide sensitivity and specificity on the order of 85%, its role in differential diagnosis is limited because it is, albeit often less markedly, also reduced in other dementias such as vascular dementia, Lewy body dementia, and frontotemporal dementia.[173,174] Alzheimer's disease–related changes in the concentrations of other Abeta isoforms are more modest.[173]

The total concentration of tau protein in the CSF is significantly increased in patients with AD with respect to controls already in early stages of the disease.[172-176] However, while it can distinguish patients and controls with sensitivity and specificity above 80%, its role in differential diagnosis is very limited because the total concentration of tau protein is elevated in a wide spectrum of disorders including stroke, multiple sclerosis, and some tumors, in addition to other dementias. On the contrary, high

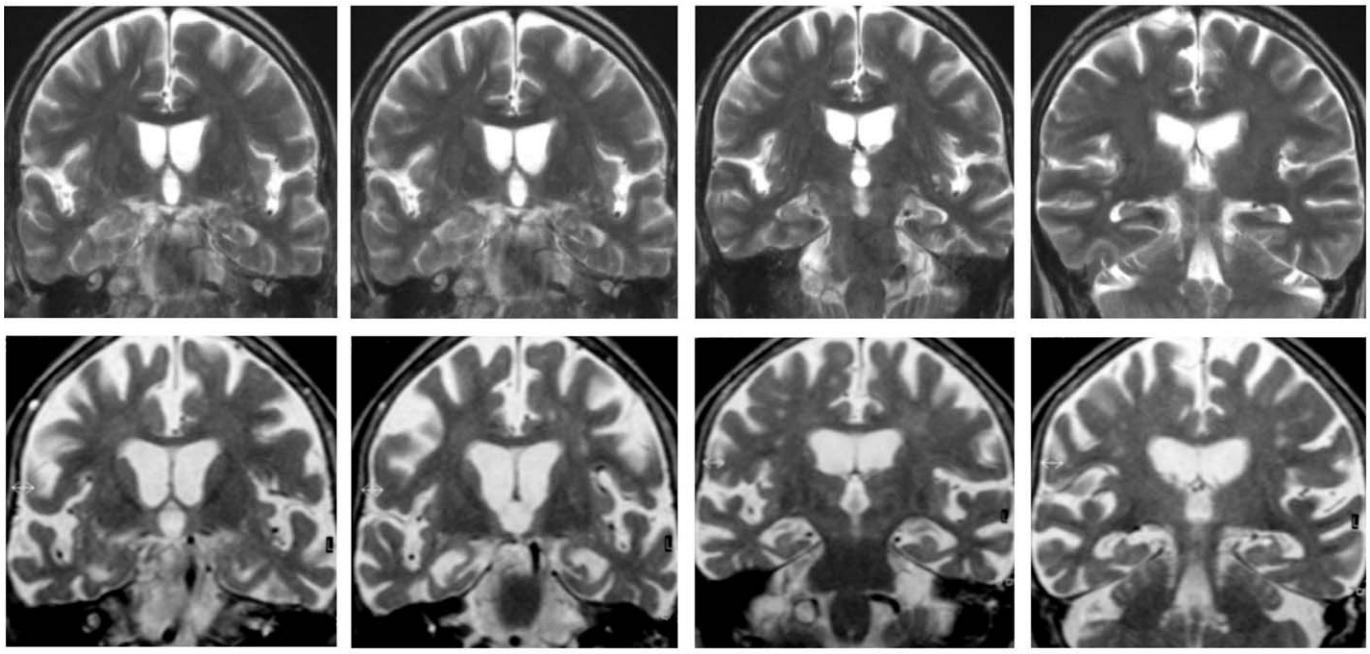

Figure 4. Structural magnetic resonance imaging (MRI). Coronal T2-weighted sections of a patient with severe Alzheimer's disease (AD; lower row) and of a healthy age-matched 75 years old control (upper row). Severe atrophy of the hippocampus, parahippocampal and fusiform gyri, and diffuse atrophy of the temporal neocortex are clearly noticeable. The temporal horns of the lateral ventricles are grossly enlarged. Courtesy of Dr A Erbetta.

concentration of phosphorylated tau protein appears to be a more specific marker of AD.[172-177]

There is growing consensus on the usefulness of measuring the CSF concentrations of phosphorylated tau protein and Abeta(42) as adjuncts to clinical diagnosis, but the viability of these biomarkers may in some cases be limited by the costs, potential risks, and patient discomfort associated with performing a lumbar puncture.

Magnetic Resonance Imaging

The role of visually-assessed structural neuroimaging with computed tomography (CT) and magnetic resonance (MR) is usually limited to ruling out secondary causes of dementia.[178,179] As shown in Figure 4, structural magnetic resonance imaging (MRI) reveals atrophy of the hippocampus and of the entorhinal cortex. In contrast with the limitations of visually-assessed imaging, MR volumetry can distinguish AD patients and controls with sensitivity and specificity around 80%; across studies, the volume of the hippocampus is reported to be reduced by about 10% in early AD, by 20% to 30% in mild AD and by more than 30% in moderate AD. Volumetry also reveals differences in the annual rate of hippocampal atrophy, between 2% and 6% for patients with AD as opposed to less than 2% for controls, and in the rate of entorhinal atrophy, about 8% in patients.[179] Furthermore, serial measurements may enable prediction of which patients with MCI will convert to AD.[180]

In patients with AD, ^{1}H-MR spectroscopy (^{1}H-MRS) reveals decreased concentration of *N*-acetyl-aspartate, a marker of neural density and viability, and elevated concentration of myoinositol, a marker of gliosis and potentially also of dysfunction of inositol metabolism.[178] Combined use of MR volumetry and spectroscopy can provide a diagnostic accuracy as high as 90%, but, as reduced *N*-acetyl-aspartate is a very unspecific finding and increased myoinositol is also characteristic of stable MCI, the contribution of spectroscopy to differential diagnosis is still a matter of debate.[178,181,182]

Diffusion-tensor imaging (DTI) reveals increased diffusivity, indicating rarefaction of the cellular matrix, and reduced fractional anisotropy, indicating reduced axonal density and integrity, in temporal, frontal, and parietal white matter.[183-186] Diffusivity and, according to some authors, fractional anisotropy correlate with clinical dementia ratings.[185,186] Diffusion imaging may also have a role in predicting which patients with MCI will develop AD.[187]

Noninvasive perfusion MRI reveals reduced cerebral blood flow (CBF) in parietal and cingulate areas (in line with SPECT and PET studies, see next section), correlating with memory scores and with the MMSE.[188,189] There is good agreement among functional MRI (FMRI) studies reporting diffusely reduced activation at encoding stage, and, in mildly impaired patients, increased activation at retrieval stage, likely paralleling encoding failure and subsequent compensatory attempts.[178,190,191] Functional MRI also provided strong evidence of abnormal memory-related activation patterns in asymptomatic carriers of the APOE ε4 allele, demonstrating that pathological changes begin to accumulate several years prior to the appearance of clinically-detectable symptoms.[191,192] Functional MRI also enables the study of the effects of cholinergic enhancers, revealing increased activations correlating with improved memory performance after single-dose administration.[193,194] It also reveals dysfunctional default-mode functional connectivity during resting state.[178,195]

Structural as well as functional MRI can provide potentially useful biomarkers and recent proposals for revised diagnostic criteria include them alongside clinical assessment, however at present their viability is somewhat limited by the fact that data postprocessing requires specialized teams and can be considerably time consuming.[168]

Nuclear Medicine

Perfusion studies with SPECT reveal reduced CBF in temporal, parietal, and posterior cingulate regions.[196] Perfusional abnormalities in temporoparietal associative regions have been found with good consistency, but there is still controversy as to whether the observed hypoperfusion in the medial temporal lobe is real or a partial voluming artifact due to atrophy.[196,197] Despite extensive clinical experience in the use of SPECT to support the clinical diagnosis of AD and confirmations of its validity from pathological studies, its role remains somewhat controversial mainly due to the poor spatial resolution and to the fact that temporo-parietal hypoperfusion is not specific to AD.[196,198] However, recent studies indicated that CBF levels in posterior cingulate and parieto-occipital areas are significantly different between AD and other dementias, and that SPECT may also have a role in predicting the conversion from MCI to AD.[199-201]

Positron emission tomography with ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) measures glucose metabolism, which can be reduced as a consequence of synaptic loss, metabolic dysfunction, and loss of projections from remote cortical areas. In agreement with perfusion SPECT, it reveals hypometabolism in parietotemporal associative areas and in posterior cingulate areas.[202,203] Although several studies failed to detect hypometabolism in the hippocampus, this appears to result mainly from methodological limitations; thanks to its superior spatial resolution with respect to SPECT, PET also enables assessment of the metabolic status of the entorhinal cortex.[204,205] In the early stages of the disease, ^{18}F-FDG PET can have sensitivity and specificity on the order of 90%; it is also potentially valuable in predicting the conversion from MCI to AD and in the differential diagnosis with other types of dementia.[206-209] However, at the time of writing PET is still seldom used in clinical practice relative to SPECT, mainly due to limited availability and to higher costs.

In a quest to further improve the diagnostic accuracy of PET, during recent years 4 amyloid-binding PET radiotracers have been developed and tested in patients: ^{18}F-1,1-dicyano-2-[6-(dimethylamino)-2-naphtalenyl] propene (^{18}F-FDDNP), *N*-methyl [^{11}C] 2-(4'-methylaminophenyl)-6-hydroxybenzothiasole (also known as Pittsburgh compound B, ^{11}C-PIB), 4-*N*-methylamino-4'-hydroxystilbene [^{11}C] (^{11}C-SB13) and 2-(2-[2-dimethylaminothiazol-5-yl]-ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole (^{11}C-BF-227).[210-213] A review of the characteristics of these tracers can be found in the article[214] by Nordberg. ^{11}C-PIB, which binds to fibrillary Abeta, was found to accumulate in regions known to contain large amounts of plaques and, in a study on mild AD patients, retention in neocortical areas was 40% to 90% higher than control values.[211]Figure 5 exemplifies the magnitude of the contrast typically observed between a patient and a control subject. Although it can be useful in distinguishing AD from other dementias not accompanied by accumulation of Abeta such as frontotemporal dementia, the role of ^{11}C-PIB PET in monitoring disease progression remains debated.[215-216] A similar tracer, ^{11}C-SB13, accumulates with an analogous pattern in temporoparietal and frontal cortical regions.[212] By contrast, ^{18}F-FDDNP, which binds to neurofibrillary tangles in addition to amyloid plaques, is characterized by higher retention in the hippocampus and in the amygdala, but the overall uptake difference between patients and controls is smaller than that obtained with ^{11}C-PIB.[210]

Nicotine labeled with ^{11}C has also been used, revealing reduced density of nicotinic acetylcholine receptors in frontal and temporal regions in the AD

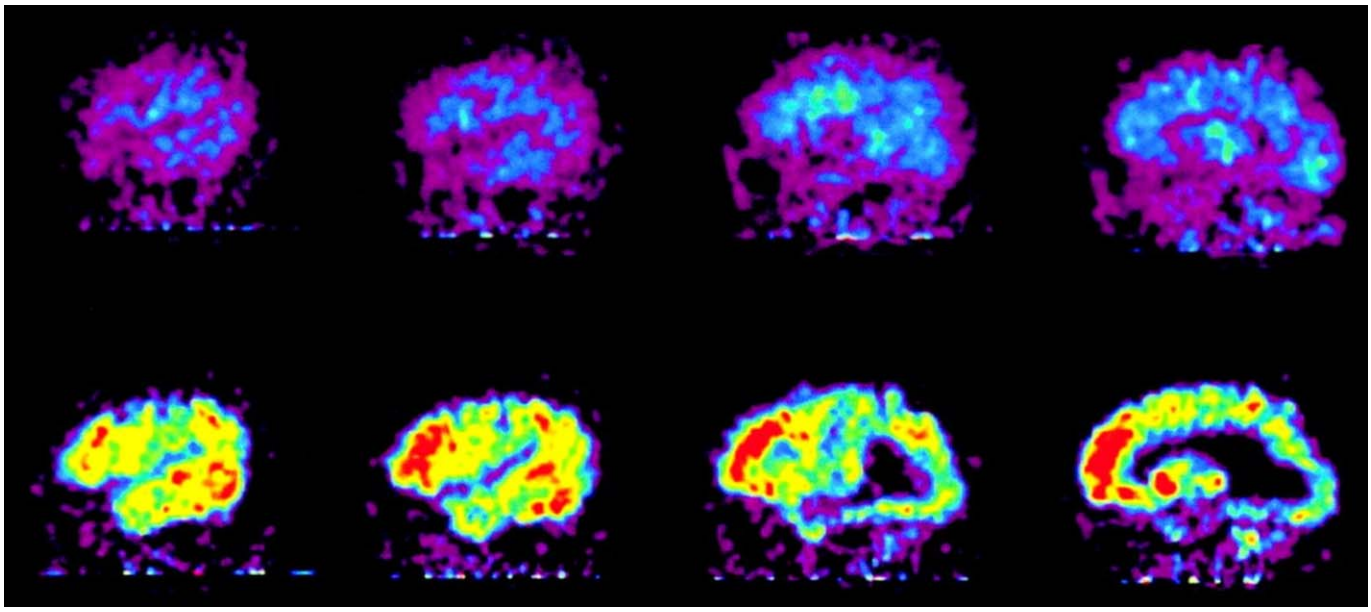

Figure 5. Sagittal planes demonstrating markedly different levels of ^{11}C-PIB retention in a healthy volunteer (upper row) and in a patient with mild Alzheimer's disease (AD; lower row), for whom uptake was highest in frontal and parietal cortical regions. Reprinted from Klunk et al[21], with permission of John Wiley & Sons, Inc. Copyright (2004) American Neurological Association.

brain, in agreement with the known loss of cholinergic innervation.[217]

Electrophysiology

Visually-assessed electroencephalography (EEG) reveals diffuse slowing, corresponding to reduced amplitude in the α (8-12 Hz) and β (12-30 Hz) bands and increased amplitude in the θ (4-8 Hz) band.[218-220] These changes are primarily a consequence of diminished excitability of cortical neurons following loss of cholinergic innervation from the basal forebrain, and correlate with the severity of cognitive impairment.[220] Despite some studies suggesting a diagnostic accuracy in the order of 80%, the predictive value of EEG appears generally limited due to overlap between healthy elderly, MCI, and patients with AD.[221] Nevertheless, EEG can be valuable in the differential diagnosis between AD, depressive pseudo-dementia, and frontotemporal dementia.[219,222]

Novel signal analysis methods reveal decreased complexity of the EEG signal, reflecting a combination of neuronal loss, disconnection, and inactivity, supporting the differentiation of AD from normal variability.[219] Analysis of signal coherence among channels reveals reduced functional connectivity in the α and β bands, indicating cortical disconnection and correlating with the severity of cognitive impairment.[223] At present, the potential of EEG-based biomarkers appears lower in comparison with MR and nuclear medicine techniques; however, if advances in signal analysis techniques improved its diagnostic accuracy, widespread equipment availability and considerably lower operational costs would be important advantages in terms of viability for use in clinical practice.

Even though their clinical usefulness is limited by large variability across sites and individuals, event-related potentials (ERPs) can have an important role in the characterization of the processing dysfunctions which underlie specific cognitive deficits.[224] There is good consistency among studies showing that middle-latency ERPs representative of early sensory processing, such as the visual P1 and the auditory N1 (both occurring at about 100 ms after stimulus administration), are unaltered in amplitude and latency until very advanced stages of the disease.[224] Results on the P2, a component occurring at about 200 ms representative of the transition between early sensory and higher cognitive processing, are more variable.[224-226] Alterations have been reported more consistently for the auditory N2, a frontal-central component occurring between 200 ms and 350 ms.[224-227] The P3, a complex component occurring between 300 ms and 600 ms and related to attentional processing and working memory load, has smaller amplitude and longer latency in patients with AD, for example when

elicited using auditory odd-ball and visual target detection tasks.[227-229] The N4, a left-lateralized component occurring between 300 ms and 600 ms and indexing semantic expectancy, also tends to have smaller amplitude and longer latency in patients with AD.[230,231]

Current and Emerging Therapeutic Approaches

Cholinergic Enhancers

The contribution of the dysfunction of the cholinergic system to the cognitive symptoms of AD became clear in the early eighties, soon after the publication of Katzman's editorial, and cholinergic enhancement was among the first treatment options to be explored. As opposed to other approaches such as the administration of acetylcholine precursors and muscarinergic agonists, inhibition of acetylcholine degradation was soon found to be a viable route.[2,232-234]

At the time of writing, 3 inhibitors of cholinesterase are available for treatment of AD, namely galantamine, donepezil, and rivastigmine. Galantamine and donepezil selectively inhibit acetylcholinesterase, which is the prominent mechanism of acetylcholine hydrolysis in the brain, while rivastigmine also inhibits butyrylcholinesterase.[235-237] In addition to its effect on acetylcholinesterase, galantamine also acts as an allosterically potentiating ligand of nicotinic receptors, increasing the strength of the residual acetylcholinergic synapses.[238]

Because of the main mechanism of action, therapy with cholinesterase inhibitors is not expected to significantly alter the accumulation of underlying pathology; it can only temporarily mitigate symptoms, and termination of treatment is generally associated with rapid deterioration to placebo levels.[233,234] According to some studies, however, long-term use of donepezil may slow disease progression.[239]

There is good consistency among studies demonstrating modest improvement of cognitive symptoms in about 30% to 40% of patients with mild-to-moderate AD. Results obtained using the MMSE (1-4 points) and the ADAS-Cog (1-3 points) are generally confirmed by subjective reports of patients and caregivers. Positive effects have been consistently observed at 6 months after treatment initiation and, according to some studies, may continue for up to 2 years.[240-245] According to the British Association for Psychopharmacology there are no differences in the level of evidence for use of galantamine, donepezil, and rivastigmine for treatment of the cognitive symptoms of AD.[245]

The usefulness and rationale of long-term treatment with cholinergic enhancers, especially in absence of improvement of cognitive functions, remains a matter of debate and ethical consideration. Despite the fact that the attainable improvements are intrinsically limited by the extensive accumulation of Abeta and tau protein pathology throughout the cortex and the hippocampal formation, cholinergic enhancement remains a topic of active research and recent years have been characterized by increased efforts directed at the development of allosteric modulators of acetylcholine receptors.[246]

Memantine

A wide range of neurodegenerative diseases including AD, Parkinson's disease, and Huntington's disease are characterized by sustained overactivation of the *N*-methyl-D-aspartate (NMDA) glutamate receptors. Their chronic, tonic overactivation impairs synaptic plasticity and, probably due to increased intracellular accumulation of calcium, leads to neuronal degeneration.[247,248] The clinical usefulness of conventional NMDA antagonists is severely limited by the side effects caused by interference with the physiological role of glutamate signaling. On the contrary, memantine appears to reduce sustained low-level activation without interfering with the physiological function of the NMDA receptors, thanks to its voltage-dependent action.[249] Several trials showed modest positive effects on cognitive and behavioral symptoms in patients with moderate-to-severe AD.[250,251] Although there is controversy over the entity of the advantage, there is good agreement among studies showing that memantine can be safely combined with cholinesterase inhibitors.[252] As for cholinesterase inhibitors, there is currently no evidence that memantine alters the accumulation of Abeta and tau protein pathology.

Treatment of Behavioral Symptoms and Nonpharmacological Interventions

Galantamine, donepezil, rivastigmine, and memantine have all been found to mitigate the behavioral disturbances occurring in moderate AD, thanks to their effect on general cognitive function and on the cholinergic afferences and reciprocal serotonergic connections of the limbic system.[253-257] To date no specific medications are available for treatment of the behavioral symptoms of AD and clinicians frequently

prescribe small doses of a range of anxiolytic, anticonvulsant, antipsychotic, and antidepressant agents.[258,259]

Atypical antipsychotics are in use, but their efficacy remains debated, especially in mild-to-moderate AD, and the risk of considerable side effects such as parkinsonian symptoms and tardive dyskinesia may outweigh the benefits.[260] In fact, in a recent trial the withdrawal of neuroleptics did not have a detrimental effect on the functional and cognitive status of the majority of patients with mild-to-moderate AD.[261]

Because of their anticholinergic properties, tricyclic antidepressants are generally not considered for treatment of depression in patients with AD.[262] By contrast, thanks to their more specific action and good tolerance, selective serotonin reuptake inhibitors (SSRIs) such as citalopram, fluoxetine, and sertraline are in widespread use. Although the number of prospective studies of the efficacy of SSRIs in AD is still relatively small, there is some consistency across studies showing reduced depression and behavioral disturbances, in the context of a general functional improvement in activities of daily living, without a significant effect on cognition.[263-266]

Nonpharmacological, evidence-based interventions and individualized holistic approaches, such as the introduction of individual and group-based structured activities, psychological therapies, cognitive rehabilitation, environmental manipulation, and caregiver education and counseling have an integral role in preserving and improving behavior, cognitive function, and psychological well-being.[267-270] Combinations of cognitive strategies, such as spaced retrieval, vanishing cues, and errorless learning, based upon preserved implicit memory function, the use of external memory aids, cognitive stimulation therapy, group-based reminiscence therapies, based on differential effects of individual and group-based social and reminiscence activities, have proven successful in maximizing memory function in individuals with AD.[271-274] In addition, person-centered therapeutic interventions that contribute to improving the social psychology milieu can reveal the emotional underpinnings of many behaviors associated with AD, enabling the evaluation of potential coping strategies and alleviating caregiver and patient distress.[275,276]

Insights from Epidemiology

Epidemiological studies have shown that the prevalence of AD is lower in patients under long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), prompting their consideration as candidate preventive or therapeutic drugs.[277] In contrast with the null results obtained in trials of cyclooxygenase 2 (COX-2) selective inhibitors, phase-II trials of (R)-flurbiprofen (Tarenflurbil) in mild AD reported a significant slowing of the deterioration of cognitive and behavioral symptoms.[277-279] Several nonexclusive potential routes of action of NSAIDs on the pathogenesis of AD have been identified: one is related to their primary activity on cyclooxygenase (COX), resulting in decreased microglial activation and concentration of inflammatory cytokines, another is the allosteric modulation of γ-secretase activity, leading to reduced production of Abeta(42) in favor of the less toxic Abeta(40), an effect which is independent of COX activity and not common to all NSAIDs.[280]

Early epidemiological studies found lower prevalence of AD in long-term statin users, but findings are heterogeneous and a recent meta-analysis did not confirm any beneficial effect; furthermore, 2 recent neuropathological studies on long-term statin users reported contrasting findings.[281-284] The putative protective role of statins cannot be explained solely by their effect on cholesterol, and recent studies have shown that they may inhibit association of APP with the cell membrane, slow the production of BACE1, and reduce inflammation.[285-287] Evidence available to date does not enable reaching firm conclusions on their potential usefulness in AD.

Some studies suggested a protective role for postmenopausal estrogen therapy. Although the hypothesis of a link with AD pathogenesis is supported by reports that, in-vitro, estrogen acts as a neurotrophic factor and affects APP metabolism, epidemiological findings are heterogeneous: some meta-analyses found reduced risk, but firm conclusions cannot be reached due to methodological issues.[288-292] The Women's Health Initiative Memory Study (WHIMS), a large prospective trial on about 4500 women, reported strongly negative results.[293]

It has also been hypothesized that the antioxidant action of vitamins C and E may have a protective effect. The Cache County study reported that elderly users of vitamin supplements had a reduced risk of developing AD over a 3-year period, but other studies failed to replicate this finding.[294-296]

Secretase Modulators

The assumption that accumulation of Abeta is an early event in the pathogenesis of AD led to the α-, β-, and γ-secretases becoming obvious targets for drug

research: upregulation of α-secretase, downregulation of β-secretase, and modulation of γ-secretase are all potentially viable approaches.

Transgenic mouse models of AD overexpressing ADAM10 display drastically reduced accumulation of Abeta, confirming the potential usefulness of α-secretase enhancement.[297] One way to potentiate α-secretase is through muscarinic agonists such as AF267B, whose efficacy has been confirmed in mice and rabbits and which also reduces tau protein phosphorylation; human trials are currently in their initial phase.[298] A potential alternative is retinol (vitamin A), which can upregulate ADAM10.[299]

The complementary approach, inhibiting β-secretase, currently appears more problematic, because BACE1-knockout mice display alterations in synaptic plasticity and behavior likely caused by failure to process non-APP substrates of BACE1. Although the physiological functions of BACE1 and of its homologue BACE2 remain largely unknown, these enzymes are widely expressed throughout the body.[28,29,300] In the hope that clinically-relevant effects could be obtained at nontoxic doses, several groups are actively developing BACE inhibitors.[301,302]

Nonselective inhibition of γ-secretase is not an option due to its role in the cleavage of several important substrates such as Notch. However, modulating its activity to decrease the formation of Abeta(42) in favor of shorter, less toxic isoforms has been demonstrated to be a viable approach.[303] To date, the most advanced γ-secretase modulator is (R)-flurbiprofen (Tarenflurbil), which is a COX-inactive variant of an NSAID (see previous subsection). Significant effects on cognitive function without severe side effects have been obtained in phase II trials on patients with mild AD. Several phase III trials are currently ongoing; recently presented results from one of them indicate no beneficial effect on cognition and daily living scores in patients with early AD.[278,279,304] Several other γ-secretase modulators are currently being developed or undergoing phase I trials.[303]

Inhibitors of Abeta Aggregation

Another therapeutic target is the complex process of aggregation of Abeta, which leads from soluble Abeta fragments and oligomers to fibrils, and ultimately plaques. Tramiprosate (3-amino-1-propanesulfonic acid, Alzhemed) has been shown to inhibit this process by interfering with the binding between Abeta and the glycosaminoglycans that promote its aggregation, reducing in-vitro Abeta toxicity.[305] A phase II clinical trial demonstrated stabilization of cognitive performance in mild AD over 36 months and the absence of significant side effects, however, due to methodological issues, phase III trials have thus far been inconclusive.[306,307] Furthermore, recent studies identified potential problems: there appear to be multiple independent pathways active in the formation of Abeta plaques, and tramiprosate appears to promote abnormal intra-axonal aggregation of tau protein.[308,309]

Immunotherapy

The first immunotherapy approach to be used was active vaccination. Initial findings showed a drastic reduction in the density of Abeta plaques in APP transgenic mice.[310] After an uneventful phase I trial, a phase II trial was started on 300 patients with mild AD. Even though no major improvement in cognitive performance was found, there was a trend toward slower cognitive decline, especially in patients with a robust antibody response. Unfortunately, the trial had to be interrupted because about 6% of patients developed aseptic meningoencephalitis.[311] Refined forms of active vaccination are still considered potentially viable and phase I trials are under way.[312]

The majority of efforts have, however, been diverted toward passive vaccination. Monoclonal antibodies have been shown to decrease Abeta plaque pathology and to reduce behavioral impairments in transgenic mice.[312,313] At the time of writing, a phase III clinical trial is under way for an antibody, bapineuzumab, which has been shown to bind to both soluble and insoluble Abeta; preliminary reports from the phase II trial indicate clinically significant activity. One phase II and two phase I trials of other antibodies are also currently under way.[312]

Inhibitors of Tau Protein Phosphorylation

Despite the fact that the exact link between Abeta and tau protein pathology remains elusive, glycogen synthase kinase-3 (GSK-3) is widely believed to play a central role, because it has been shown that it can be activated by Abeta and that it can hyperphosphorylate tau protein.[314,315] One GSK-3 inhibitor that is receiving increasing attention is lithium, which has been shown to reduce the phosphorylation of tau rotein and to enhance its binding to microtubules.[316] Lithium also appears to affect Abeta production, but results are discordant: a research group reported that it activates β-secretase without affecting γ-secretase but another found that it modulates γ-secretase favoring the production of shorter fragments. Another GSK-3

inhibitor, SB415286, was reported not to increase Abeta production.[317,318] Notably, in addition to potentiating α-secretase, some muscarnic agonists seem to inhibit GSK-3.[319] In parallel with attempts to reduce the activity of kinases, other possible strategies include activating phosphatases and inhibiting the aggregation of tau protein into tangles.[234] As yet unpublished preliminary results from a Phase II trial suggest a considerable slowing of cognitive decline in individuals with mild and moderate AD treated with methylthioninium chloride, a tau protein aggregation inhibitor.

Nerve Growth Factor

Another promising approach is to deliver nerve growth factor (NGF) to support the survival of the cholinergic basal forebrain system.[320] In the first trial, NGF protein was administered by intraventricular injection to 3 patients with AD. Although the trial had to be halted due to side effects, improved blood flow, metabolism, EEG, and cognitive function were found in 1 out of the 3 patients.[321] In a more recent phase I trial, modified fibroblasts expressing human NGF were implanted in the basal forebrain and widespread metabolic and perfusional improvements were found, together with decreased rate of cognitive decline in the absence of significant side effects.[322]

Summary and Future Prospects

The cholinergic hypothesis, according to which the symptoms of AD are predominantly caused by dysfunction of acetylcholine signaling, was initially conceived in the early 80s. Supported by compelling evidence of severe degeneration of the basal cholinergic neurons and by results obtained with scopolamine models, it formed the backbone of AD drug development until the last decade. At the time of writing, cholinergic enhancers remain by large the most widely prescribed drugs for AD.[323]

Nowadays, the amyloid cascade hypothesis is the basis of the development of the majority of putative disease-modifying therapies. As discussed in the second section, multiple independent evidences provide support for this view. However, no experiment has yet formally tested the model and several questions of crucial importance remain open. What are the mechanisms leading to Abeta accumulation in sporadic AD? Altered expression of APP, unbalanced α-secretase and β-secretase activity, altered γ-secretase activity, and inefficient Abeta degradation and clearance are all possible and clearly nonmutually-exclusive candidates. What is or what are the primary pathogenic factors? Is Abeta accumulation the result of a primary dysfunction or of an aberrant compensatory attempt?

Even though the toxicity of Abeta is well-established the exact mechanisms remain unknown. Fibrillary forms were originally believed to be the primary neurotoxic species but in recent years evidence on the toxicity of Abeta oligomers has also accumulated.[36] Although we do have evidence of Abeta toxicity in vitro and in vivo, single-transgenic mouse models of AD, despite massive accumulation, do not robustly develop neurofibrillary tangles.[42] This may simply reflect a limitation of the models or it may signal a need to refine the simple, linear view placing tau protein pathology as a consequence of Abeta toxicity.

Despite the current focus on Abeta pathology, there is also a considerable number of research groups pursuing different strategies and developing novel therapies targeting acetylcholine, glutamate, GABA and serotonin signaling, inflammation, nitric oxide signaling, histamine and cannabinoid receptors, mitochondrial function, axonal transport, and cell-cycle regulation.[324]

Currently available diagnostic techniques provide a considerable range of biomarkers with varying levels of accuracy, cost, and availability. At the time of writing, many are severely underutilized and the diagnosis of AD remains, in most cases, essentially clinical. The main reason is the palliative nature of currently available treatments, which do not generate a pressing need for improved diagnostic accuracy. The development of effective disease-modifying agents will lead to consideration of a wide range of laboratory, imaging, and electrophysiological biomarkers for use in everyday clinical practice.

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