

EARLY RECOGNITION AND TREATMENT OF DEMENTIA

Overview

Alzheimer's disease is the most common form of dementia in persons over the age of 65. The confirmatory diagnosis of Alzheimer's requires an autopsy examination that manifests classic histopathology findings including senile plaques, neurofibrillary tangles, and amyloid deposition. The brain for each patient with Alzheimer's disease contains a variable mixture of senile plaques, neurofibrillary tangles, dystrophic neurites, synaptic loss, and amyloid deposits. Although senile plaques are considered the pathological hallmark of Alzheimer's disease, neurofibrillary tangles are more specific for dementia than senile plaques.

Clinical and neuro-radiological research on the boundary between normal age-related memory loss and early dementia provides valuable insight into the earliest stages of Alzheimer's disease.

Scientists define four intellectual categories for older persons: 1) normal {NL}, 2) age-associated memory impairment {AAMI}, 3) mild cognitive impairment {MCI}, and 4) dementia {AD} **See**

Table 1. The diagnosis of dementia require a careful clinical history, mental status exam, physical assessment, neurological examination, and appropriate laboratory testing to exclude metabolic problems. Brain imaging, i.e., PET and SPECT, enhance the predictive value of clinical history or genetic testing. Sophisticated, electrophysiological studies may also prove useful. Present best practice bases diagnosis on a thorough clinical history.

Table 1

The Spectrum of Cognitive Loss

<u>Stage</u>	<u>C/O</u>	<u>Testing</u>	<u>Imaging</u>
NL	--	NL	--
Age-related forgetfulness	+	NL	--
MCI	+	ABNL	+
Dementia	+	ABNL	+

MCI-EARLY RECOGNITION

The human brain reaches full development by age 25 years and remains stable until age 45-55 when subtle age-related brain changes occur in the cerebral cortex and brainstem. The microscopic hallmarks of Alzheimer's disease include: senile plaques, neurofibrillary tangles, amyloid deposition, and synaptic loss. The senile plaques and amyloid deposition commence sometime after age 50 and these accumulations accelerate after age 65. Neurofibrillary degeneration occurs later than senile plaques; however, most individuals over the age of 65 have a few neurofibrillary tangles in the mesial temporal cortex, i.e., hippocampus, amygdala. Almost

all individuals over the age of 85 have some senile plaque, amyloid deposits, and/or neurofibrillary tangles. Large numbers of intellectually intact individuals over the age of 90 will have conspicuous amounts of amyloid in the brain. Prospective studies show that 5-10% of cognitively intact elders will meet autopsy criteria for Alzheimer's disease. The hippocampus is most consistently damaged in aging and disease.

The hippocampus is a 3.0cm segment of specialized cortex situated on the medial aspects of both temporal lobes. The human hippocampus processes new information and encodes short-term memory. The hippocampus and adjacent temporal cortices are affected earliest with age-related brain changes. Senile plaques, neurofibrillary tangles and synaptic loss within the hippocampus produce the characteristic short-term memory loss associated with Alzheimer's disease. Brain imaging studies can detect subtle volume loss and metabolic reduction in this structure.

Older patients may demonstrate a range of cognitive impairments. Most older individuals have no memory problems while some older individuals complain of difficulty with retaining large volumes of new information. Older, "forgetful" individuals have normal neuropsychological testing as well as normal brain imaging and this memory complaint is referred to as age-associated memory impairment. These first two groups of elders are considered to have normal cognitive function. A third group of older individuals with mild cognitive impairment (MCI) demonstrate mild intellectual loss that includes subtle deficits on neuropsychological testing and mildly reduced scores on intellectual screens such as the mini-mental status examination. MCI, an isolated amnesic syndrome may develop into dementia and the new clinical entity, is the focus of intense clinical research. Individuals with MCI scores between normal or mildly impaired on many dementia rating scales and these individuals may demonstrate subtle abnormalities of brain imaging in the mesial temporal cortex. Individuals with MCI develop dementia at 12% per year in contrast to 1-2% of normal individuals over age 65; however, a small group of MCI patients never develop dementia.

The fourth group of individuals are those with clinically diagnosed dementia. Demented persons have clear cognitive loss in two or more intellectual domains, e.g., amnesia and aphasia, but almost all Alzheimer's patients demonstrate short-term memory deficits. Most demented persons score poorly, i.e., below 22, on the MMSE but some demented individuals with high premorbid intellect may score in the borderline range, i.e., 22-26. Individuals with MCI lose 1.0 point per year on the MMSE in contrast to mild dementia patients who lose 2.5 points. Patients with moderate/severe disease will lose 3.5 points per year.

Early recognition of mild, cognitive impairment (MCI) provides a therapeutic opportunity for clinicians. Preliminary, clinical studies suggest that therapeutic intervention in the MCI stage will slow cognitive decline and prolong function beyond improvements seen with early treatment of mild dementia. Cholinesterase inhibitors, e.g., Aricept, Exelon, are presently prescribed for MCI patients. Vitamin E, Gingko, and other "preventive" interventions may also provide protection against progression of the disease.

All present and future therapy will focus on early recognition and treatment of Alzheimer's disease. Subtle cognitive deficits may exist 7-20 years prior to onset of disease. Although these preventive therapies will not eliminate dementia, treatment may significantly reduce morbidity and disability associated with this disease.

Other types of dementia may begin with insidious loss of memory function; however, a careful, clinical evaluation will usually provide information that suggests dementia other than Alzheimer's. Diagnostic accuracy for dementia exceeds 90% for careful, experienced clinicians **(See Table 2)**.

Table 2. COMMON, IMPORTANT, EARLY MANIFESTATIONS OF DEMENTIA IDENTIFIED BY A BASIC EVALUATION

TYPE	SEVERITY OF EARLY COGNITIVE LOSS	SEVERITY AND TYPE OF EARLY PSYCHIATRIC SYMPTOMS	ASSOCIATED MEDICAL PROBLEMS	COMMON NEUROLOGICAL FINDINGS	ASSOCIATED LABORATORY FINDINGS
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Alzheimer's	Moderate *Amnesia	Mild *Anxiety *Depression	None	None	None
Vascular	Moderate	Moderate *Depression *Psychosis	Hypertension Cardiovascular Disease	Focal Deficits	Strokes on CT
Alcoholic	Mild	Moderate *Apathy	Alcoholic Heart, liver, pancreas or peripheral nerve damage	*Ataxia *Sensory Loss	Abnormal: Liver, blood, indices
Diffuse Lewy Body	Moderate *Fluctuating	Moderate *Visual hallucinations *Fluctuating symptoms	None	Parkinsonism	None
Fronto-temporal Dementia	Mild	Moderate *Apathy *Personality changes	None	None	None

Any kind of dementia can produce any combination of symptoms. Some patients have mixed dementia.

MOLECULAR BIOLOGY OF ALZHEIMER'S

a. Neuropathology

The aging human brain manifests Alzheimer's-type changes after age 50 and most persons over age 65 have some Alzheimer's-type pathology. The microscopic pathology of Alzheimer's disease includes: 1) senile plaque, 2) neurofibrillary tangles, 3) abnormal, dystrophic neurites, 4) amyloid deposits, and 5) synaptic loss. The mesial temporal cortex, including the hippocampus with entorhinal cortex region, manages short-term memory. Mesial temporal cortical structures are consistently damaged in both Alzheimer's disease and normal aging; however, hippocampal circuits require severe damage before short-term memory impairment occurs. The presence of plaques and amyloid cores in human brain does not predict a clinical history of cognitive decline. Substantial numbers of normal persons over the age of 90 have high levels of amyloid and a discreet group of cognitively intact elders demonstrate high densities of senile plaques; however, high densities of neurofibrillary tangles are almost always present in persons with dementia. Since the degree of synaptic loss is difficult to measure, the relationship between synaptic damage and dementia is unclear.

The long-range treatment strategies for Alzheimer's disease follow two basic paths based on the type of brain pathology. The senile plaque is linked to amyloid, while the neurofibrillary tangles are connected to a cytoskeleton protein called tau. A neurofibrillary tangle is a mass of filamentous material present inside the cell body of individual neurons. A senile plaque is a focal disruption of brain tissue caused by deposition of amyloid, abnormal processes and perhaps inflammatory response to the brain damage outside neurons. Dystrophic neurite are abnormal neuronal processes that contain abnormal cytoskeletons. Synaptic loss is reduction in numbers of specialized connection between neurons; especially prominent on the dendrites. The pathological diagnosis of Alzheimer's disease is based on the intensity of pathology rather than the mere presence of any particular microscopic abnormality.

b. Amyloid Theory

Amyloid is an abnormal protein produced by abnormal processing of this substance that is normally present in neuron membranes. A large amyloid precursor protein (APP) is cut into smaller protein fragments that are either normal, i.e., beta amyloid 39, or abnormal, i.e., beta amyloid 42. The enzymes that cut β APP are termed "secretases". The anti-amyloid strategies include blocking the production of abnormal amyloid fragment, i.e., Ab42, accelerating production of normal amyloid, i.e., Ab39, and accelerating the degradation of abnormal amyloid. The role of amyloid in the pathogenesis of Alzheimer's disease remains unclear. Mice can be genetically manipulated to over-produce amyloid and these animals develop amyloid deposits within the brain. Vaccination of these genetically engineered mice with the abnormal amyloid protein results in diminished amyloid deposition and fewer amyloid cores. This supposed "vaccine" for Alzheimer's disease may provide some therapeutic benefits; however, the unvaccinated mice do not develop true Alzheimer's disease, i.e., senile plaques, neurofibrillary tangles, and synaptic loss. Moreover, many intellectually normal elders have substantial amounts of amyloid.

c. Tau Theory

Each neuron contains a delicate mesh-work of fibrils and tubules within the cell body termed cytoskeleton. The neuronal cytoskeleton constantly undergoes production and degradation. Neurofibrillary tangles and dystrophic neurites are produced by abnormalities of cytoskeletal metabolism. Reduction of abnormal amyloid deposits may not slow the development of either neurofibrillary tangles or dystrophic neurites. Neurofibrillary tangles are linked to abnormal production and phosphorylation of the microtubule-associated protein tau, which require specific

enzymes, i.e., proteases, that are under investigation. Pharmaceutical companies are investigating compounds that block the abnormal phosphorylation of tau and consequently the development of neurofibrillary tangles or other associated neuronal abnormality.

Researchers conclude that two distinct pathways exist for the molecular neuropathology of Alzheimer’s disease, i.e., tau and amyloid. This brain disorder is far more complex than abnormal amyloid deposition. Moreover, the distinction between normal “brain aging” and Alzheimer’s disease is obscure.

GENETICS

The role of genetics in the pathogenesis of Alzheimer’s disease remains confused. Chromosome 1 and 14 are linked to the autosomal dominant form of this disease that accounts for a tiny percentage of all Alzheimer’s disease. Abnormalities on chromosome 21 are linked to the high rate of Alzheimer’s disease in patients with Down’s Syndrome because the amyloid gene is situated on this gene. Chromosome 10, 12, and 19 are linked to the sporadic familial type of Alzheimer’s disease. The scientific consensus points to a substantial genetic component in Alzheimer’s disease. Although many neurotransmitters are depleted in Alzheimer’s disease, acetylcholine is consistently lost in most patients. Alzheimer’s patients experience cholinergic depletion early in the disease and severe cholinergic loss usually occur in the late stages. Cholinesterase inhibitors such as Aricept (donepezil), Exelon (rivastamine), and Reminyl (galantamine) enhance the amount of acetylcholine and slow the progression of the disease (See Table 3). All of the cholinesterase inhibitors have been demonstrated to prolong patient function and slow the necessity of nursing home placement. Enhanced cholinergics has slowed AIDS.

function may also decrease behavioral complications (See Table 4). Cholinesterase inhibitors work in the early and mid stages of the disease when mini-mental scores exceed 15. The therapeutic benefit of cholinesterase inhibitors may exceed simple enhancement of brain cholinergic levels and these compounds may promote synaptic survival or increase production of trophic factors, e.g., nerve growth factors that facilitate plasticity within

	Typical Effective Dose	Effective for AD	Side Effects
Aricept (Donepezil)	5-10	Yes	Mild
Exelon (Rivastigmine)	6-12	Yes	Mild to Moderate
Reminyl (Galantamine)	16-24	Yes	Mild

Table 4
The Impact of Cholinesterase Inhibitors on Symptoms in Early Dementia

<u>Medication Effect</u>	<u>Intensity of Improvement</u>	<u>Numbers of Patients Affected</u>
Cognitive Improvement	Minimal	Few
Cognitive Stabilization	Substantial	Most
Side Effects	Mild	Minority
Behavioral Improvement	Mild	Minority

surviving neurons. The overall efficacy of cholinesterase inhibitors is similar; however, side effect profiles may differ. Donepezil i.e., Aricept, may have fewer GI side effects than other medications, however, all of these compounds are reasonably well tolerated. Cholinesterase inhibitors do not improve cognitive function but these medications slow progression. Stabilized patients should not be switched to other cholinesterase inhibitors unless the patient is experiencing side effects. AD patients on cholinesterase inhibitors should continue with therapy until all valuable cognitive function is lost. Abrupt withdrawal of cholinergic medications may precipitate abrupt cognitive decline that is irreversible with resumption of cholinesterase inhibitors. Dose tapers or drug holidays are not indicated in well-controlled patients.

Neuronprotection

Vitamin E treatment slows the onset of dementia symptoms by almost one year. Large doses, i.e., 2,000 units per day of vitamin E were used to demonstrate the effect and other free radical scavengers may also prove beneficial. Many clinicians use doses of 1000 units per day, as the long-term effects of high dose Vitamin E therapy are unknown.

Table 5

	<u>Dose</u>	<u>Prevent Onset</u>	<u>Slow Progression</u>	<u>Recommend</u>
Vitamin E	1000 units/day	+	+	Yes
Estrogen	Routine Replacement Dose	+	---	Yes
NSAIDS	Routine Dose	+	?	No
Ginkgo	40mgm TID	?	?	?

Estrogen may have a protective effect in women. Studies in large numbers of older women suggest those who receive estrogen prior to onset of dementia may have a diminished risk for developing Alzheimer's disease. Estrogen has several other potential benefits in women to include protection against osteoporosis and cardiovascular disease. The risk for endometrial tumors as well as breast cancer limits the use of this hormone in some individuals. Large multi-center prospective studies are presently underway to measure the effect of estrogen on cognition.

Ginkgo Biloba, a European herbal remedy, may have beneficial effect in dementia. Several studies suggest this medication slow progression although recent studies dispute this observation.

Inflammation

Non-steroidal anti-inflammatory medications (NSAIDS), such as the ibuprofen or COX-2 inhibitors, may diminish the risk for developing Alzheimer's disease. Anti-inflammatory medications may limit the inflammatory response within the brain to amyloid deposits or neurofibrillary tangles. The risk of drug-induced medical complications, e.g., gastrointestinal bleeding, outweighs the possible preventive benefits of these medications. The possible therapeutic value of NSAID therapy is limited to persons with mild impairment.

Dementia Prevention

The treatment of Alzheimer's disease is further complicated by the growing recognition of mixed dementias. Many patients with Alzheimer's disease also have diffuse Lewy body-type changes or ischemic damage to the brain. A growing body of scientific evidence suggests that dementia may result from the cumulative loss of synaptic contacts within the brain produced by multiple diseases,

e.g., Alzheimer's, strokes, etc. Individuals with high lifetime intellectual achievement are less likely to develop dementia. Lifetime intellectual stimulation may increase synaptic reserves and increase the amount of brain damage required to produce clinical/functional deficits. Diseases that further reduce neurons and synaptic densities may accelerate the onset of Alzheimer's disease. Patients who develop dementia following stroke, i.e., post apoplectic dementia, frequently have Alzheimer's disease at autopsy. Although the stroke is contributory, the dementia was produced by the Alzheimer changes. Many patients with both cardiovascular/cerebrovascular disease and Alzheimer's disease may benefit from preventive strategies that minimize ischemic damage to the brain, e.g., anticoagulants, anti-platelets, exercise, etc. Older individuals who exercise regularly and avoid depression are at reduced risk for dementia.

Although a few studies suggest that neurons may continue to reproduce in the mature brain, this theory is disputed and the number of regenerating neurons is probably small. Brain regeneration remains a treatment for the distant future. The present focus of therapeutic strategies is prevention of neuronal or synaptic loss rather than neuronal regeneration. Aging neurons retain some plasticity and therapeutic strategies may also promote reinnervation of empty dendritic fields by adjacent neurons. Even over age 75, human neurons, e.g., hippocampus, retain the ability to extend dendrites into brain regions left vacant by neuronal death. Exogenous trophic factors, e.g., nerve growth factor, may play an important role in sustaining function through facilitation of such brain repair.

A definitive cure for Alzheimer's disease will probably involve genetic testing for at-risk populations and preventive therapies commencing at age 40-60. Additional therapeutic strategies will focus on promotion of early neuronal repair and reduction of neuronal damage from other diseases such as cerebrovascular insufficiency. These future therapeutic strategies will require that healthcare systems recognize at-risk populations or mild dementia as well as encourage the populations to take long-term therapies that prevent an invisible disease.

The available research on Alzheimer's disease concludes that: 1) the pathological distinction between age-related pathology versus Alzheimer's disease is obscure, and 2) treatment is only effective when initiated early in the disease. The future direction for dementia treatment may focus on these individuals with subtle, early, subclinical dementia. Large multi-center studies are examining the effect transmitter enhancements or neuro-protection to reduce the risk for developing dementia. Future management strategies may include screening for mild, cognitive

impairment with subsequent, sophisticated brain imaging, blood testing or genotyping, and consequent aggressive multifaceted preventive therapies.

Alzheimer's disease was previously thought to be untreatable and incurable. The clinical pessimism that characterized the 80's has now been replaced by measured optimism about our ability to alter the natural history of this disease.

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Objectives:

1. Describe the pathological continuum between aging and Alzheimer's disease
2. Explain the distinction between age-associated memory impairment, mild cognitive impairment, and dementia
3. Discuss the role of cholinesterase inhibitors in the treatment of Alzheimer's disease
4. Describe the use of neuro-protective agents in slowing the progression of Alzheimer's disease
5. Discuss future treatment strategies for the management of Alzheimer's disease

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