Diagnosis and Management of Alzheimer's Disease - An Update

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Summary

Alzheimer's disease (AD) has become recognised as a major cause of morbidity and mortality in the ageing population worldwide. Over 20 million people worldwide are affected by AD, which ensures that the disease imposes a major economic burden. Alzheimer's disease is a progressive neurodegenerative disorder with characteristic clinical and neuropathological features. Neurofibrillary tangles, neuritic plaques and amyloid angiopathy occur in varying severity in brains of patient's with Alzheimer's disease. Biological markers of AD allowing an early definitive premorbid diagnoses are currently not available. Memory loss for recent events is invariable and often the earliest prominent symptom. Language disorders, difficulties with complex tasks, depression, psychotic symptoms and behavioral changes are other common manifestations of AD. Diagnosis involves the early detection of cognitive decline and ruling out other causes of dementia like vascular dementia, Lewy body dementia, fronto-temporal degeneration or reversible causes like hypothyroidism.

Acetylcholinesterase inhibitors have shown to be effective in mild to moderate AD in improving the cognitive function of patients in clinical trials. Caregiver intervention programs have considerable potential to improve both the caregiver and patient quality of life.

Key Words: Alzheimer's disease, Dementia, Acetylcholinesterase inhibitors

Introduction

On the 4th November 1906, at the 37th Conference of South-West German Psychiatrists in Tubingen, Dr. Alois Alzheimer, a German neuroscientist gave a landmark lecture in which he described the symptoms of one of his patients, Mrs Auguste D., a 51 year old women who had shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. At autopsy, her brain showed evidence of plaques, neurofibrillary tangles and arteriosclerotic changes. The eponym Alzheimer, originally used to refer to presenile dementia has later come into use for the largest cause of dementia in the elderly accounting for 50 - 60% of the cases of late onset cognitive deterioration. Lewy body dementia and vascular dementia are responsible for the majority of the remainder, followed by frontotemporal degeneration.

Epidemiology

Large studies in many countries have shown that Alzheimer's disease (AD) is common and increases exponentially with ageing. The prevalence rate shows that approximately 5% of those affected are 65 years and above and 20% of those over 85 years are affected at any time. The prevalence of dementia among the Chinese >= 65 years in age has been found to be lower (1.7% to 4.6%) than those found in Western countries and in Japan. AD was the most common type of dementia.
found among most Chinese in community surveys. There is an estimated prevalence rate of 6% of dementia among the elderly Malays in an urban settlement in Malaysia compared to a prevalence rate of 4% in Malays and 2.3% in Chinese staying in Singapore. Increasing age has been a significant risk factor for dementia in the majority of community surveys, female gender, low educational background and head trauma have been found to be risk factors only in some studies. Family history has been found to be another significant risk factor and as shown by Li et al, AD has a significant association with family history of dementia in first degree relatives. A significant association between the apolipoprotein E4 allele (apoE4) and AD has been found among Chinese as well as among Caucasians. Apart from apolipoprotein E (APOE), alpha2 macroglobulin (A2M) has also been identified as a robust late onset AD risk factor. However, 3 genes have been associated with the rare early onset familial AD: the amyloid precursor protein (APP) gene on Chromosome 21, the presenilin-1 (PS-1) on Chromosome 14 and the presenilin-2 (PS-2) gene on chromosome 1.

Neuropathology
The brain in AD is markedly atrophied and the histological hallmarks are neuronal loss, neuritic amyloid plaques, neurofibrillary tangles and amyloid angiopathy. Aggregation of amyloid seems to be the central event leading to neuronal toxicity and cell death which is most marked in the area of the brain that acts as a source for neurons using acetylcholine as a transmitter- the nucleus basalis of Meynert in the medial temporal lobe.

Neurochemically the change most characteristic of AD is severe deficiency of choline acetyltransferase, the enzyme that catalyses the synthesis of acetylcholine. Aggregation of the amyloid in the brain is further facilitated by the Apolipoprotein E4 and the presence of the E4 allele on the chromosome 19 is a risk factor for the late onset familial and sporadic AD. Each copy of E4 brings forward the age of onset of AD by 4 - 5 years.

Clinical Features
The clinical spectrum of AD can be quite varied and divided into three progressive stages: early, middle and late stages of 2 - 3 years each. AD is a progressive degenerative disorder with a highly variable rate of deterioration in intellectual function leading to death after about 10 years.

Cognitive Changes
The cardinal neuropsychological deficit in AD is amnesia or memory loss which is most prominent for recent events. Early signs of memory loss include making numerous lists and making repeated phone calls to relatives. Eventually memory loss worsens until the patient is unable to use lists or keep any of his appointments and misidentifies own family members. Early signs of language difficulty include occasional difficulty in finding words (nominal dysphasia) and diminished fluency in speech. In later stages of the disease the patient with AD is increasingly repetitive, unable to follow conversation and finally has complete loss of coherent speech. The earliest signs of difficulty in complex tasks or dyspraxia include difficulties in dressing and personal hygiene. In later stages the patient with AD is unable to carry out other activities of daily living like bathing or toileting. The ability to recognise objects and faces (agnosia, prosopagnosia) is often lost. The patient often gets increasingly lost even in a familiar environment and as the topographical disorientation worsens, patients may even be unable to find their way from the living room to the kitchen in their own home. Driving skills may be lost in the early stage of the disease and early inquiry of the patient’s driving skills must be made from the family.

Depression and Psychotic Symptoms
Symptoms of depression are common and frequent in the early stages of AD but as the clinical detection is difficult, studies show varying rates-ranging from 25% to 85% in patients with AD. Simple delusions of theft are commonly encountered in patients with AD. Mistaken beliefs have a prevalence rate of between 10 - 30% in different studies.

Personality and Behavioral Changes
Early in the disease there is a narrowing of interests and activities with the patient exhibiting disengagement, indifference and diminished affection. In later stages the most frequent behavioral disturbances include wandering and agitation occurring in 70% of patients, aggression and violence in 20% of patients.
Diagnostic Evaluation

Alzheimer's disease (AD) is a diagnosis by exclusion. Three sets of internationally recognised guidelines have been used to establish the diagnoses - DSM (IV)\textsuperscript{20}, CERAD\textsuperscript{21} and the NINCDS-ADRDA\textsuperscript{22} criteria. The latter are the most widely used and the diagnoses of probable AD is based on deficits in 2 or more cognitive areas, progressive decline in cognition, no disturbance in consciousness and onset between 40 - 90 years of age with the absence of systemic disorders that could account for the dementia. Supporting features would include deterioration in language, motor skills and perception, impaired ADL's, altered behavior, family history and cerebral trophy on CT scan. The diagnosis of possible AD is applied to patients with presenting symptoms consistent with AD, if there is a systemic or brain disease that could cause cognitive deficits but is not considered as the cause of dementia. The diagnosis of definite AD is appropriate only when clinical criteria are met and neuropathologic evidence can be documented from biopsy or autopsy.

Clinical Evaluation

History

An evaluation of the patient with probable AD begins with a thorough medical, neurologic and psychiatric history usually from a caregiver who has most contact with the patient. The pattern of onset of cognitive abnormalities and the temporal course of the disease can help differentiate AD from the dementia secondary to vascular causes\textsuperscript{23}. Changes in function should be inquired from assessing the ADL in all patients and the nature of impairments determined. Changes in personality or behavior are often easily obtained in history taking as they are the most disturbing and difficult to handle by the caregiver. A history of the patient's occupation or hobbies (especially any changes from the previous level of function) may provide clues on the effect of illness on social and occupational function. A family history of drug and alcohol use, past medical history of systemic illness and any risk factors for stroke or ischemic heart disease must be sought.

Cognitive Scales

The Mini-Mental State Examination\textsuperscript{24} (MMSE) is the most widely used cognitive screening test. Although scores may be influenced by language, socioeconomic status, and ethnicity, age and education have the greatest effect on the result\textsuperscript{25-26}. The CAMCOG is the cognitive subscale of a comprehensive global assessment procedure which is used in Europe\textsuperscript{27}. The ADAS-cog\textsuperscript{28} is the cognitive subscale of another global assessment procedure widely used in USA and in clinical trials.

Functional Scales

The Progressive Deterioration Scale (PDS) was developed by DeJong and colleagues\textsuperscript{29} as one of the first prospective, AD-specific instruments able to measure changes in functional autonomy associated with this neurodegenerative condition. The PDS was developed to measure reliably the functional changes seen in AD patients as they move from one disease stage to another, with the knowledge that the loss of ability to accomplish simple daily activities greatly affects the quality of life of the patients.

Global staging scales provide a useful measure of overall disease severity and an overall estimate of clinically meaningful change over the longitudinal course of a disease with or without treatment intervention. The most widely used scales are the GDS\textsuperscript{30} and the Clinical Dementia Rating scales (CDR)\textsuperscript{31}. In clinical practice assessment can be made by direct observation or by caregiver interview and the assessment of function need not be dependent upon the above scales. However the scales are useful both in repeated assessment as a measure of change and to ensure complete assessment.

Behavioral Assessment

Scales to measure the behavioral disturbance and the non-cognitive symptoms of AD are used mainly in research and clinical trials. Such scales include the Behavior Pathology in Alzheimer's Disease Rating scale (BEHAVE-AD)\textsuperscript{32}, the Consortium to Establish a Registry for Alzheimer's Disease Behavior rating scale (CERAD-BRSD)\textsuperscript{33} and the Neuropsychiatry Inventory (NPI)\textsuperscript{34}.

Physical Examination

In early AD the patient usually does not seek medical help on his own. He is brought to the doctor's office by relatives who have noticed memory loss or personality change. The patient does not look ill and often full physical and neurological examination reveals no
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abnormalities. The patient has a tendency to look at his relatives or caregivers when any questions are asked by the doctor: "The Head Turning Sign". Very occasionally in early AD, primitive reflexes such as glabellar, grasp and snout reflexes may be present.

However the presence of atypical clinical features suggestive of non-AD include neurological findings of abnormal voluntary movements, localizing signs, amyotrophy, seizures, cerebellar ataxia or peripheral neuropathy. As the severity of AD increases, extrapyramidal signs in conjunction with gait disturbances can be found. In the terminal stages, patients with AD are bedridden, markedly stiff, incontinent and are almost mute with little response.

Psychiatric Evaluation
Depression and dementia may often coexist in elderly patients especially in the initial stages of AD. When the diagnoses for AD is suspected, patient should undergo assessment for depression and vice versa. Evaluation of depression in AD patients can be done by using scales like the Cornell Scale for Depression in Dementia or the Columbia Scale for Psychopathology in AD (CUSPAD). In selected group of patients neuropsychologic testing may be necessary for the diagnosis of cognitive decline and these tests can provide additional data when decisions regarding driving, safety, occupation and competence must be made. Normative data on the commonly used neuropsychologic tests have become available to assess performance in older subjects.

Laboratory Evaluation
Most of the diagnostic laboratory tests for AD do not provide much information of the disease but can help to exclude other causes of dementia. The laboratory tests recommended by the American Academy of Neurology include full blood count, ESR, blood urea, serum electrolytes, creatinine, liver function tests, serum vitamin B12, syphilis serology, thyroid screen, urinalysis and HIV testing (selected patients).

Neuroimaging
Computed Tomography (CT) without contrast is sufficient for detection of most of the reversible dementias caused by large structural lesions. Although the majority of patients with AD may show a high degree of atrophy in the medial and temporal lobes with ventricular enlargement, these CT findings alone cannot confirm or exclude the presence of AD nor distinguish between AD and normal ageing. Magnetic resonance imaging (MRI) is more sensitive than CT for evaluating atrophy, vascular lesions and lesions adjacent to the bone. However access can be limited and costs are high, limiting its usage in the assessment of AD only to tertiary centres. Recently the Dementia Research Group in U.K. have developed a method of serial MRI scanning which provides a very robust measure of brain atrophy over time. It is based on using a computer to superimpose precisely each volume image on its predecessor, then measure change by means of digital subtraction. AD patients can lose up to 15% of their brain volume in three years. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) demonstrate decreased glucose metabolism and blood flow in the temporoparietal region in the early stage AD. PET is a powerful tool for the evaluation of functional changes in the brain and may help in the early diagnoses of AD prior to CT/MRI changes or cognitive defects. Recently PET has been used to detect cholinergic deficits at the early stages of the disease by measuring acetylcholinesterase activity in the brain.

Cerebrospinal fluid (CSF) analysis
Tau is a normal axonal protein and an increase in CSF-Tau is believed to reflect ongoing neuronal and axonal degeneration or damage. An increase in CSF-Tau in AD has been confirmed in numerous studies. The sensitivity and specificity for CSF-Tau to identify AD was above 70 - 80%. Hence determination of CSF-Tau seems helpful as an aid in the clinical diagnoses of AD.

Treating Alzheimer's Disease
A) Non-Pharmacological Management
1. Managing the family
It is important after a thorough assessment to arrive at a specific diagnosis based on the available criteria. Once the diagnosis is reached the physician would be able to discuss at length regarding the nature of the disorder, likely prognosis and the complications that could arise.
as the disease progresses. Caregivers must be provided with as much information regarding AD to help them in caring for their relations with AD. Caring can induce much stress within whole families as well as individuals, resulting in strained relationships between siblings and patients or the children. Caregiver intervention programs which involve psychological support educational aspects and the development of a support system, have considerable potential to improve both the caregiver and patient quality of life.

2. Managing the environment
New environments often exacerbate the confusion in AD and hence the patient should be kept in as familiar surroundings as possible. An occupational therapist assessment of the home is essential as the AD progresses to improve safety aspects. There may be a need for home modifications or extra physical aids may be required. Physicians should often inquire from the family about driving safety and advise the patient when to stop.

3. Managing the patient with behavioral disorders
Behavioral problems associated with AD include agitation, aggression, resisting help from carer's, wandering, incontinence, sleep disturbances, and emotional liability. These "non-cognitive" problems are often frustrating, disruptive and often deteriorate the quality of life of the patient, increase the caregiver stress and accelerate the need for long term care in nursing homes. Many behavioural disturbances may often be attributable to coexisting illnesses, sensory impairment (visual or auditory), environmental or social factors. The behaviour of subjects with dementia represent an attempt to express feelings and needs that cannot be adequately verbalised. Management of problem behaviour can then be shifted from trying to change the patient to modifying the causative or exacerbating factors as described in detail by Carlson et al. In the majority of cases, behavioral disturbances can be managed by a behavioral approach using the mnemonic PAID as a reminder of the causes of behavioral disturbance (Physical, Intrinsic, Activity related, Depression and Delusion). Insight oriented psychotherapy can help to improve self image, reduce anxiety, improve communication skills and reduce maladaptive behaviors.

Other techniques such as reminiscence therapy, validation therapy and reality orientation therapies are also useful. However further research needs to be done on the effectiveness of these therapies.

B) Pharmacological Treatment

Neuroleptics
Phenothiazines especially haloperidol are prescribed for AD patients to reduce agitation, hallucinations and other intractable behavioral disturbances. In view of the anticholinergic activity and side effects of these drugs they must be started in low doses and increased slowly.

Hypnotics
Benzodiazepines can increase the confusion in patients with AD and if possible must be avoided. If behavioral methods to improve sleep hygiene fail, then shorter acting agents like lorazepam or oxazepam which lack active metabolites are useful.

Antidepressants
Selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression in elderly subjects. In view of the limited efficacy of neuroleptic agents and the presence of serotonin deficiency in the brain of patients with AD, a trial of SSRIs could be considered in patients with behavioral problems especially if depressive symptoms are present. However SSRIs like fluoxetine or paroxetine hydrochloride may aggravate symptoms of anxiety or agitation in patients with AD and must be used with caution.

Cholinergic Agents
One of the most significant advances in the treatment of AD has been the use of acetylcholinesterase inhibitors to enhance the cholinergic transmission by inhibiting the breakdown of released acetylcholine. The first of such compounds was Tacrine which ameliorates some of the cognitive symptoms of AD but the effect was most notable in a minority of patients able to tolerate the highest dosage 160mg daily. Adverse effects limited its usage as only 31% were able to complete a 30 week study. In 50% of patients serum transaminase levels increased and in 25% the increase was three fold necessitating cessation of drug therapy.
Donepezil was introduced in 1997 when a multicentre, doubleblind, placebo-controlled trial in the United States showed that Donepezil at a dosage of 5mg once daily for 12 weeks provided significant clinical improvement in cognitive function in patients with mild to moderate AD and its administration was not complicated by peripheral cholinergic adverse events or hepatotoxicity.\(^6\) Rivastigmine is a 'pseudoirreversible' brain selective inhibitor of acetylcholinesterase, the metabolism of which is totally independent of the cytochrome P450 system. A recent international randomised controlled trial\(^7\) has shown that rivastigmine is well tolerated, effective in improving cognition, activities of daily living and global evaluation ratings in patients with mild to moderate AD. In this 6 month trial, the effects of rivastigmine were dose dependent and adverse events leading to the discontinuation of treatment were seen in 27% of patients taking 6 - 12mg/day of rivastigmine.

**Guidelines for the Treatment of AD**

The London AD treatment working group have drawn up recommendations for the drug treatment of AD.\(^8\) Prescription of drugs should be after a through assessment and the diagnosis is based on McKhann's criteria.\(^22\) Usually dementia has been present for more than 6 months and an MMSE score of 10 - 24 is used as an entry criterion for starting treatment. Evaluation of response can be considered in 3 phases: early (2 weeks) for side effects, later (3 months) for cognitive state and response. There should be continued 6 monthly evaluation of disease state on maintenance therapy. Evaluation of response should be done both by MMSE and carer's report with global assessment of functioning. Early criteria to stop treatment include poor tolerance, continued deterioration at the pretreatment rate even after 6 months or an accelerated deterioration.

Drug free periods (6 weeks) are often useful in evaluating response.

**Prognosis**

Patients with AD have an average survival of 10.3 years but the range varies from a few months to 21 years.\(^9\) As a result of the heterogeneity present in AD, the rate of progression varies from patient to patient. The presence of extrapyramidal signs is associated with more severe AD and suggests a more rapid course of disease over time.\(^6\) Data also suggests a significant relationship between the presence of delusions and impaired functional status in AD which ultimately will affect the level of independence of the patient. Factors that often predict institutionalization in patients with AD include increasing behavioral problems or increasing functional impairments and high caregiver stress/burden. One year institutionalization rates in patients with AD range from 12 to 39%.\(^6\)

**Prevention of Alzheimer's Disease**

Bonn and Tang et al\(^{62,63}\) have shown that substantial numbers of women on Hormone Replacement Therapy (HRT) had significant reduction in the risk of AD. One randomised controlled trial\(^64\) of Vitamin E supplements in the treatment of AD has shown a delay in the deterioration of dementia by an average of 8 months. A reduced risk of AD was linked in the Baltimore Aging Study\(^65\) to increased use of NSAIDs. More large scale controlled trials are needed to assess further these preventive strategies.

**Prospects for Future Therapy**

Research into the molecular biology of AD\(^66\) promises the probability of developing new disease modifying agents to reduce the deposition of amyloid and causing less plaque formation or the prevention of formation of intraneuronal neurofibrillary tangles. Three enzymes have been shown to participate in the metabolism of amyloid precursor protein (APP) and the combination of beta and gamma secretases yield fragments of proteins that can be deposited to form plaques. Drugs under development include those that enhance alpha secretase cleavage of APP and inhibit beta and gamma secretases.

Similarly new drugs which inhibit tau kinases (glycogen synthase kinase-3) and which phosphorylate tau will reduce the process of tau aggregation and hence neuronal death.

**Conclusion**

Alzheimer's disease is now recognized as an important public health problem that has devastating effects on
Both the patient and the caregivers. A complete medical and neuropsychological evaluation is necessary for older persons with memory loss or functional decline. Management of patients with AD include the treatment of behavioral disorders, pharmacotherapy with acetylcholinesterase inhibitors and supportive care for the caregivers or families of these patients. Caregiver intervention programs can reduce caregiver psychological morbidity and delay institutionalization of patients with AD.

Preventive strategies like HRT therapy for women at high risk, reduction of vascular risk factors, NSAID therapy and Vitamin E supplementation have shown promise in the reduction of risk of AD in older persons. More research is now being focussed on drugs which act as disease modifying agents which will slow or halt the progression of this devastating illness.

References

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C.M.E Quiz on Alzheimer's Disease

1. Significant risk factors for Alzheimer’s disease include:
   A. Hypercholestroleamia
   B. Male sex
   C. Family history
   D. Apolipoprotein E4
   E. Increasing age

2. Characteristic neuropathologic findings in brains of patient’s with Alzheimer’s disease include:
   A. Accumulation of aluminium deposits in the neurofibrillary tangles
   B. Intraneuronal neurofibrillary tangles but absence of amyloid plaques
   C. Deficiency of choline acetyltransferase
   D. Marked atrophy of the occipital pole
   E. Amyloid plaques are mostly seen in the area of the medial temporal lobe

3. Characteristic clinical features of Alzheimer's disease include:
   A. Nominal dysphasia
   B. Memory loss for past events
   C. Dyspraxia
   D. Agnosia
   E. Visual hallucinations

4. On physical examination of a patient with Alzheimer’s disease the following statements are true:
   A. Primitive reflexes may be present
   B. Cerebellar signs may be present
   C. No abnormalities can be detected
   D. Abnormal involuntary movements can be observed at times
   E. Occasionally a focal deficit like a gait disturbance can be detected

5. The following drugs have been found useful in improving the cognition in patients with Alzheimer's disease:
   A. Physostigmine
   B. Donepezil
   C. Neostigmine
   D. Rivastigmine
   E. Hydergine