AMSE JOURNALS –2015-Series: Modelling C; Vol. 76; N° 1; pp 1-22
Submitted June 2014; Revised Dec. 26, 2014; Accepted Feb. 20, 2015

A Review on the Early Diagnosis of Alzheimer's Disease (AD) through Different Tests, Techniques and Databases

*C.S. Sandeep, **A. Sukesh Kumar

*Electronics and Communication, Faculty of Engineering, University of Kerala
Trivandrum, India, (sandeepcs07nta@gmail.com)
** Electronics and Communication, Faculty of Engineering, University of Kerala
Trivandrum, India, (drsukeshkumar@yahoo.in)

Abstract

Gerontology deals with the many clinical problems that are common in the elderly population, and many of these follow the orthodox pattern of clinical practice. Patients characteristically have poor insight and often attribute their early symptoms of amnesia to normal ageing. Alzheimer's disease (AD) is common form of senile dementia. There are several causes for the disease. Although our understanding of the key steps underlying neurodegeneration in Alzheimer's disease (AD) is incomplete, it is clear that it begins long before symptoms are noticed by patient. Any disease – modifying treatments which are developed are most likely to be successful if initiated early in the process, and this requires that we develop reliable, validated and economical ways to diagnose Alzheimer's−type pathology. However, despite comprehensive searches, no single test has shown adequate sensitivity and specificity, and it is likely that a combination will be needed. There are lot of tests and neuroimaging modalities to be performed for an effective diagnosis of the disease. Conventional clinical decision making systems are more manual in nature and ultimate conclusion in terms of exact diagnosis is remote. In this case, the use of advanced biomedical engineering technology will definitely helpful for making diagnosis. Profiling of human body parameter using computers can be utilised for the early diagnosis of Alzheimer's disease. There are several neuroimaging techniques used in clinical practice for the diagnosis of Alzheimer's – type pathology. Prominent of them are Magnetic Resonance Imaging Scan (MRI), Positron Emission Tomography (PET) and Single Photon Emission CT Scanning (SPECT). Apart from above we are

focussing on the databases related to AD such as ADNI (Alzheimer Disease Neuroimaging Initiative) and OASIS (Open Access Series of Imaging studies) for a definite diagnosis of the disease. In this research work, it is planned to investigate techniques for the early diagnosis of Alzheimer's disease (AD) with the help of various laboratory tests, neuroimaging techniques and databases.

Key words

Alzheimer Disease (AD), neurodegeneration, MRI, SPECT, PET, ADNI and OASIS.

1. Introduction

The early diagnosis of Alzheimer's disease (AD) is the most important part for preventing the disease from its progression at the earlier stage [Sandeep C.S, Sukesh Kumar A]. Alzheimer's disease (AD) is an irreversible age related neurodegenerative disorder of the brain that leads to memory loss and impairs the ability to perform routine functions as well [Alzheimer's Association, 2010]. The impairment of normal functions not only affects the patients but the family members as well. Alzheimer's disease was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist [Alzheimer A]. In 2001, eleven million people suffered from Alzheimer's disease worldwide. At present nearly 36 (35.6) million people are believed to be living with Alzheimer's disease or other dementias, increasing to nearly 66 (65.7) million by 2030 and more than 115 (115.4) million by 2050 [Alzheimer's Disease International, 2011]. The number of people with dementia will double by 2030, and more than triple by 2050 [www.alz.co.uk]. The progression of the disease can be categorized in four different stages. The first stage is known as Mild Cognitive Impairment (MCI), and corresponds to a variety of symptoms (most commonly amnesia) which do not significantly alter daily life. Between 6 and 25% of people affected with MCI progress to AD every year. The succeeding stages of Alzheimer's disease (Mild and Moderate AD) are characterized by an increase in cognitive deficits, and a decrease in independence, culminating in the patient's complete dependence on caregivers and a complete deterioration of personality (Severe AD) [Shimokawa]. Alzheimer's disease is the sixth-leading cause of death and is 70% prevalent in all cases of dementia [AA, 2012]. According to another report every 71 sec, someone develops Alzheimer's disease and the rate doubles roughly every 10 years after age 65 [WAD, 2011].

1.1 Causes and effects of AD

Alzheimer's disease is one of the underlying causes of dementia. Dementia is the common term which indicates impaired brain functions and encompasses symptoms like memory dysfunction, leads to confusion of places and things, unable to perform routine tasks, loss of intellectual functions and impaired judgment. But, this condition is a symptom of many underlying neurological disorders including Alzheimer's disease, Dementia with Lewy Bodies (DBL), Parkinson's disease, Frontotemporal Dementia (FTD), Vascular Dementia Normal-Pressure Hydrocephalus (NPH) and Delirium or Depression. AD is the most prevalent underlying cause of dementia and is clinically evident when there is gradual loss of higher brain functions including change in behavior and personality. The symptoms related to AD may leads to disorientation and aphasia (difficulty in language), indicating cortical dysfunction, agnosia (impairment in recognizing object or things and humans), apraxia (impaired motor function) and significant of all, memory impairment. With disease progression patients suffer disability and immobility as well. The brain structure of such patients has a gross cortical atrophy with compensatory enlargement of ventricles.

The most important neuropathological hallmarks of AD are intraneuronal neurofibrillary tangles (NFTs) and extraneuronal senile plaques. Neurofibrillary tangles are filamentous bundles in cytoplasm of the neurons displacing or encompassing nucleus. In the rounder cells they appear as 'globos tangles' while in pyramidal cells, they appear as 'flame' [Frosch M.P, D.C Anthony, U.D Girolami]. Senile or neuritic plaques present outside the neuron, appears as a spherical body bearing dilated and tortuous neuritic processes around an amyloid beta core which contains some abnormal proteins like amyloid beta plaques which are derived through the processing of Amyloid Precursor Protein (APP) [Harvey R.A, P.C. Champe, B.D. Fisher]. The aggregates of amyloid beta obtained from processing of APP are difficult to degrade which consequently activate inflammatory cascade that lead to oxidative injury and alterations in phosphorylation. Genetic mutations or familial causes involved in AD pathology include mutations on chromosomes 1, 14 and 21. Other risk factors for this type of disease are advanced age, small head size, history of head trauma, lower intelligence, and female gender [Cummings J.L, H.V. Vinters G.M. Cole ,Z.S. Khachaturian, Yaari R, J. Corey-Bloom].

1.2 Tests for diagnosing AD

Some earlier tests that were conducted for AD are neuropsychological tests, Computed Tomography (CT) scans and structural Magnetic Resonance Imaging (MRI). Neuropsychological tests are mainly used for determining the specific type and level of cognitive impairment that the patient has conducted a study using various types of neuropsychological tests. A few of them that

were used include, “Rey Auditory Verbal Learning Test, Trial Making Test parts A and B, category fluency, Digit Span forward and backward, Digit Symbol Substitution Test, and the Clock Drawing task” [Larson E.B, Wang L, Bowen J.D].

CT scans were normally used to look for atrophy of the brain, and enlarged ventricle size. Firstly it was believed that cerebral atrophy was significantly higher in patients with AD than those didn’t have. However it was discovered later that healthy people also have cerebral atrophy. Patients with dementia may not have cerebral atrophy at least in the earlier stages of the disease. From these findings it was determined that it can be difficult to distinguish between a healthy elderly patient and a patient with dementia. Therefore, CT scans have been deemed as clinically not useful in the primary diagnosis of AD.

After CT was discredited, questions were raised about using structural MRI performed a study to evaluate “predictive models of progression from amnestic MCI (mild cognitive impairment) to AD to assess the additional benefits of structural MRI data compared to clinical measures alone. Structural MRI measures the “medial temporal lobe structures, ventricular volumes and whole brain volumes. This turned out resemblance to the CT scans that were done. It became really hard to differentiate between healthy patient’s brain atrophy and a patient with brain atrophy. Though we didn’t find MRI structural measures, compared to cognitive measures, to be necessary for predicting AD in subjects with moderate degrees of MCI, this doesn’t necessarily repudiate the utility of anatomic MRI as a potential biomarker for AD. Therefore MRI can be helpful in differentiating between MCI and AD [Mayeux R].

In addition, Positron Emission Tomography (PET) uses biochemical means of acquiring images rather than structural information. “PET technology involves the detection of photons by a camera-like device that records the levels of radioactivity originating from given points in space and time. Positron emitting radioisotopes are used to generate the radioactivity”. PET scan can measure different compounds in the brain, in the case of AD; PET is used to measure fluorodeoxyglucose (FDG). FDG can compete with glucose for absorption and metabolism in neurons. With dementia patients the neurons intake of glucose and FDG becomes impaired. “ By highlighting regions of decreased FDG uptake, PET can theoretically help in the diagnosis of dementia, even if there is absence of the gross structural damage detected by other imaging techniques such as CT or MRI” [Harvey R.J, Skelton-Robinson M, Rossor M.N]. PET has been used widely to study about AD, and it is evolving into an effective tool for early diagnosis. PET has been used to detect people at risk for AD even before the symptoms start. PET is a very expensive scan to perform although it has been the most useful as far as providing visual images in the detection of AD. There are some new

advances in technology that can not only detect AD, but possibly explain the symptoms and how the disease works.

All of these tests and scans can help to show the memory recall of a patient and the possible areas where the patient lacks deficiency. Using these tests can be helpful to find the types of treatment plans that can be given, however neuropsychological tests alone are not helpful in detecting early AD. Trials were then conducted combining neuropsychological tests with clinical tests and various imaging technologies. For an effective and early diagnosis of AD, a population based study is necessary and required, which gives an idea about the various tests involved in determining AD. In this paper we combine different tests and imaging modalities with different databases such as ADNI and OASIS for finding the sensitive disease progression changes in the affecting areas related to AD. The co-author's previous works in the area of Biomedical Engineering will definitely help to develop a new tool using latest biomedical methods for the solution of the early diagnosis of AD [Sukesh Kumar A, Jyothiraj V.P, Subin T.K, Sheeba O].

2. Risk factors of AD

The genetic risk in familial early-onset AD differs from that in the sporadic late-onset form of the disease. In the familial disease, the three genes implicated are all autosomal dominant, and include the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1 and the amyloid precursor protein gene on chromosome 21. Presenilin 1 gene mutations are most common among familial AD mutations. Mutations in these genes lead to an overproduction of beta-amyloid (Aβ) peptides (Aβ40 and Aβ42), which give rise to synaptic dysfunction, neurotoxicity, and Aβ deposits in the brain called neuritic or senile plaques. But in early-onset AD, is rare. In sporadic or late-onset AD, the apolipoprotein-E (APOE) ε4 allele increases the risk of developing the disease. As a susceptibility gene, the genotypes APOE ε2/ε4 or ε3/ ε4 increase the risk by approximately three-fold, and the genotype APOE ε4/ε4 increases the risk by approximately 15-fold. The population-attributable risk (ie the proportion with late-onset AD associated with APOE) is estimated to be 20%, making it the most important risk factor. The APOE allelic variants may be involved in the degradation or clearance of Aβ from the brain. Genome-wide association (GWA) studies and a recent meta-analysis of 12 GWA studies implicated three additional genes, namely the complement receptor 1 (CR1), clusterin(CLU), and phosphatidylinositol binding clathrin assembly protein (PICALM), which are novel susceptibility loci for late-onset AD in European ancestry populations.

Age is another risk factor for AD. The annual incidence of AD is approximately 1% among elderly persons aged 65 to 70 years, and increases to 6 to 8% of persons older than 85 years. The prevalence of AD is below 1% for persons aged 60 to 64 years, and increases with age to 24 to 35% among persons aged 85 years or above, and is higher in women than men [Ferri C.P, Prince M, Brayne C, Chiu H.F, Lam L.C, Chi I, Hy L.X, Keller D.M]. In men, high bioavailable testosterone levels appear to reduce the risk of AD [Chu L.W, Tam S, Wong R.L]. The risk of AD is highest among those with low or limited levels of education. A positive family history of AD occurs in around 15% of AD patients, and increases the risk of AD approximately four-fold. The relationship of alcohol use to AD follows a U-shaped relationship; moderate consumption is associated with a reduced risk, whilst in heavy drinkers and non-drinkers the associated risk of cognitive impairment, dementia, and AD appears to be increased. The protective effect of moderate alcohol intake may be related to the antioxidant properties of wine [Chan K.K, Chiu K.C, Chu L.W]. Physical activity and exercise reduce brain tissue loss, dementia, and the risk of AD, possibly via increased neurotrophic factors. Smoking increases the risk 2 to 4 times. Depressive mood and cardiovascular risk factors are also associated with an increased risk. Severe head injury also increases the risk of AD, possibly via reduced brain reserve or increases in brain Aβ deposition. Other dietary factors may also reduce the risk of AD, including vitamin B12; folate; antioxidants including flavonoids; vitamins C and E; unsaturated fatty acids; and a Mediterranean diet pattern [Scarmeas N, Luchsinger J.A, Schupf N]. There is a strong link between cardiovascular health and brain health. Having heart disease, high blood pressure or high cholesterol can increase the risk of developing AD. This is caused by damage to blood vessels in the brain, resulting in less blood flow and possible brain tissue death. Type 2 diabetes may also increase the risk for AD. Inefficiency of insulin to convert blood sugar to energy may cause higher levels of sugar in the brain, causing harm.

3. Hallmarks of AD

A definite diagnosis of Alzheimer disease can be made only by autopsy examination of a patient's brain. This neuropathological evaluation reveals gross cerebral atrophy, signifying loss of neurons. The diagnostic lesions are found on microscopic evaluation of the most affected areas of the brain, which reveal the presence of large numbers of extracellular neuritic plaques and intracellular neurofibrillary tangles, which are shown in Fig.1.

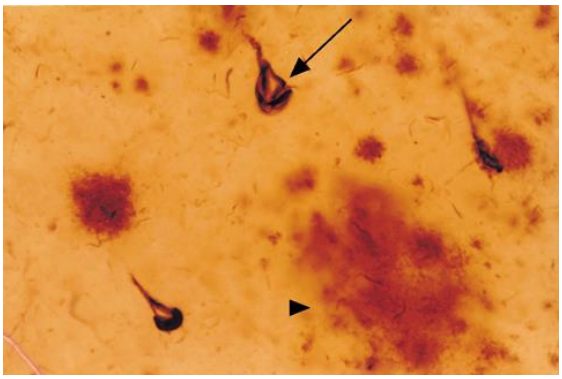

Fig.1. Light micrograph of Alzheimer disease neuropathology.

The above figure shows the section from the cortex of a patient with Alzheimer disease showing tangles and plaques. The intraneuronal tangle (arrow) is stained dark brown with an antibody that specifically targets paired helical filaments. These filaments are also seen as the dense brown material (dystrophic processes) embedded in the extracellular plaque (arrowhead). The lighter reddish staining of the plaque is from another antibody directed specifically against β-amyloid (Aβ). Plaques and tangles are found most predominantly in the temporal and frontal lobes, including the hippocampus. In most of the advanced cases, the pathology extends to other regions of the cortex, including the occipital and parietal lobes. Plaques are insoluble extracellular deposits composed mainly of a 40–43 amino acid peptide called β-amyloid (Aβ). Aβ derives from a larger protein, β-amyloid precursor protein (APP) by proteolytic processing. Plaques can be described as diffuse or classical. Diffuse plaques are amorphous aggregates of Aβ which are typically not associated with dystrophic neurons and abnormal neurites. Classical neuritic plaques contain densely aggregated Aβ and are generally associated with degeneration and neuronal cell loss. Patients with Alzheimer disease also have an increased coincidence of cerebrovascular disease, possibly related to deposition of amyloid within the cerebral vasculature, which occurs in most cases. In early-onset familial AD, excessive Aβ is formed. In late-onset AD, there is reduced clearance of the usual amounts of Aβ. The excess Aβ aggregates to form soluble dimers, trimers, and low-ordered molecules called oligomers. Further aggregations into Aβ protofibrils, fibrils and neuritic plaques may also occur. While all these forms of Aβ aggregates account for neuronal dysfunction and neuronal death in AD, Aβ oligomers are particularly toxic to the neuron. In AD, the second neuropathological hallmark is an intraneuronal accumulation of abnormally hyperphosphorylated tau(τ) (ie described as the tau hypothesis). Apparently, this impairs normal transport function and causes aggregation of the tubules to form NFTs within the neuronal cell in the transentorhinal regions, hippocampus, amygdala, and then neocortical association areas. Tangles

are intracellular deposits of the microtubule associated protein tau (τ) found within dystrophic neurons. Tau is normally found in great abundance in neurons, where it binds tubulin monomers together to form stable polymers that are presumed to be essential in cellular transport and axonal growth. In Alzheimer disease tangles, the tau becomes hyperphosphorylated and this leads to less efficient binding to microtubules. The unbound tau then spontaneously aggregates into insoluble paired-helical filaments, which are seen as deposits in the neurons. While plaques and tangles do occur in normal ageing brains, they are more numerous and more widely distributed in brains of patients with Alzheimer disease. The determination of whether plaques and tangles cause neuronal degeneration or are simply markers of it is essential for designing effective treatment strategies.

3.1 The behaviour of plaques and tangles in AD

Although the role of plaques and tangles in AD is still not known precisely, they are found in greatest abundance in the areas of the brain most affected in Alzheimer disease, namely the hippocampus, temporal cortex, frontal cortex and parietooccipital cortex. The hippocampi are small sea-horse-shaped structures nestled in the temporal lobes, which play a central role in establishing and maintaining memory. The hippocampi show the earliest changes in Alzheimer disease and have the highest concentration of plaques and tangles. This finding corresponds to the early and progressive symptoms of memory loss in patients with AD. The development of plaques and tangles in cortical areas correspond to the other clinical findings seen in Alzheimer disease, including abnormal visuospatial orientation, difficulty with skilled tasks and language abnormalities. The progressive loss of neurons and neuronal interconnections, known as synapses, is associated with a decrease in the concentrations of neurotransmitters, the chemical signals that are sent between neurons. One such neurotransmitter is acetylcholine, the decline of which is hypothesized to be one of the factors responsible for the intellectual deterioration seen in both normal ageing and in Alzheimer disease. There is a dramatic decrease in the levels of choline acetyltransferase, the enzyme needed for the synthesis of acetylcholine, in Alzheimer disease brains as compared with controls. For this reason, there has been much interest in developing drugs that increase the level of acetylcholine in the brain as a treatment for AD.

4. Early diagnosis of AD

In AD research in the last 20 years while much has been accomplished, a great deal remains to be done to improve its diagnosis and treatment in the early stage. There is increase evidence that early diagnosis of Alzheimer disease will be the key factor to maximize treatment benefits. But

frequently, patients are diagnosed in later stages of the disease, when disabling symptoms and neuropathological changes have become well established. AD affects a considerable and increasing part of the population. Despite the lack of disease-modifying treatment at present, discovering sensitive and specific markers of early AD would be a major breakthrough as it would allow us to slowdown or perhaps even arrest the degenerative process before dementia develops. Furthermore, current symptomatic treatments, such as acetylcholine esterase inhibitors, may be more efficient when administered in the early stages of AD. The diagnosis of clinically probable AD can currently be made in living subjects only once the stage of dementia has been reached. It is based on a number of criteria as defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), but can only be confirmed by postmortem histopathology [McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E.M]. While the clinical signs of AD are well established, the early symptomatic and predementia stage remains to be better defined.

4.1 Preliminary tests to diagnose AD

In practice, a clinical diagnosis of AD is made when patients have progressive memory decline for over 6 months with a resulting impairment of selfcare and social or occupational functioning. The presence of objective memory impairment should be documented by the Mini-Mental State Examination (MMSE) and other neuropsychological tests. Other essential diagnostic points include deficits in two or more areas of cognition, absence of disturbance in consciousness, disease onset between the ages of 40 and 90 years, absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition, evidence of cerebral atrophy on computed tomography (CT) or magnetic resonance imaging (MRI) without other significant organic lesions, and absence of any metabolic disorder [American Psychiatric Association; 1994]. In most patients, the above information can be obtained after a detailed history from the carers, physical examination, and cognitive tests that measure memory, language skills, and activities of daily function related to brain functioning. An early, accurate diagnosis of AD is especially important to patients and their families. It helps them plan for the future and pursue management options, while the patient can still take part in making decisions. During the diagnostic process, it is also crucial to rule out other causes of cognitive decline, particularly other types of dementia. Vascular dementia, frontotemporal dementia, and Lewy body dementia need to be considered as possible subtypes in the differential diagnoses. Structural neuroimaging (CT or MRI) can help rule out the presence of strokes, subdural haematoma, normal pressure hydrocephalus or tumours. Serum vitamin B12 level,

red blood cell and serum folate levels can help exclude these deficiencies. Abnormalities in these tests, however, are quite common in elderly persons, and may or may not be causal. Overall, AD accounts for 65% of all patients with dementia, while secondary causes explain a minority. Vascular dementia (VaD) and mixed AD-VaD are usually the second and third most common causes, respectively. In general, this clinical approach is often employed in conjunction with established diagnostic criteria for AD, including those in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD [McKhann G.M, Knopman D.S, Chertkow H]. Using the latter criteria, the term "probable AD" is equivalent to the clinical diagnosis of AD during a lifetime, as definite AD can only be only made at postmortem. Experienced clinicians can diagnose AD with approximately 90% accuracy. The addition of biomarkers, in particular, amyloid (eg Pittsburgh compound B or PiB) positron emission tomography (PET) and fluorodeoxyglucose (FDG) PET brain scans can further improve diagnostic accuracy (Figs 2 and 3).

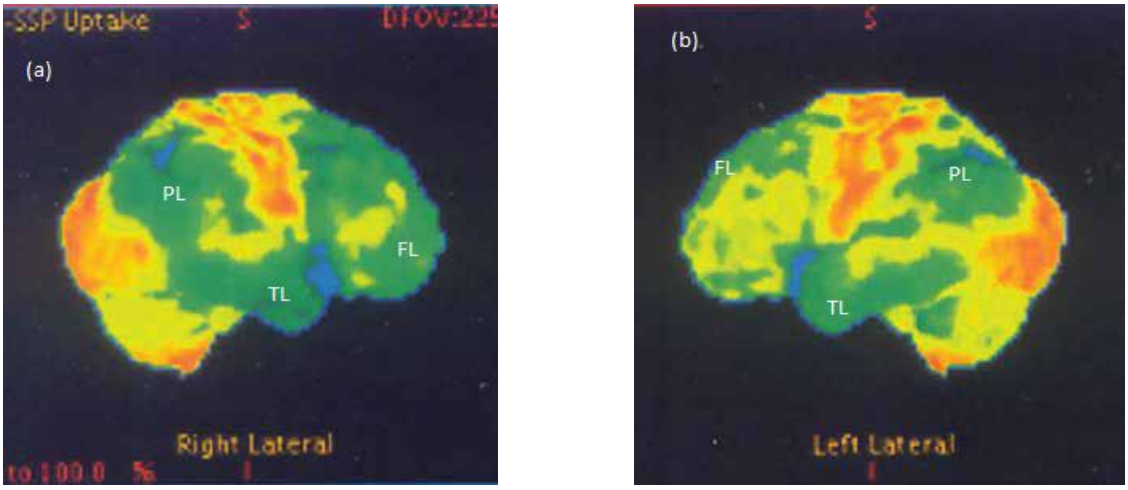

Fig.2. Fluorodeoxyglucose positron emission tomography (FDG PET) brain scan in Alzheimer's disease (AD) Brain FDG PET scan in moderately severe AD: right lateral (a) and left lateral (b) symmetrical hypometabolism affecting temporal (TL), parietal (PL), and frontal (FL) lobes

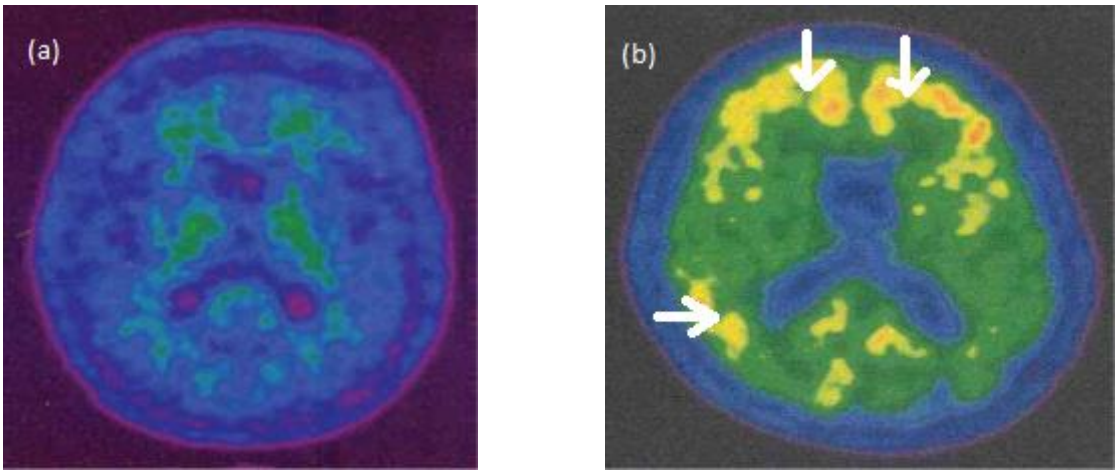

Fig.3. Pittsburgh compound B (PiB) positron emission tomography (PET) brain scan in Alzheimer's disease (AD) and normal controls (a) Normal older adults without AD: PiB-negative, with no PiB retention in cerebral cortex. (b) AD patient: PiB-positive (white arrows), with moderate PiB retention in frontal and parietal cortic

4.2 Biomarkers of AD

Alzheimer's disease is now regarded as a chronic disorder type of disease. Affected patients have neuropathology in their brains for over 10 to 20 years before symptoms occur. With ongoing research to develop new AD treatments, an increasing need to establish an early diagnosis of AD could become important. Thus, biological markers which could allow a positive diagnosis early in the course of AD appear desirable. Amyloid PET brain imaging and low cerebrospinal fluid (CSF) Aβ42 levels constitute neuropathological biomarkers, reflecting Aβ protein deposition in the brain. The second group of biomarkers reflects neuronal degeneration, injury, and brain atrophy. These biomarkers include structural MRI regional brain atrophy (in the hippocampus, medial, basal and lateral lobes, and the parietal lobe), decreased [^{18}F]FDG PET uptake in the temporoparietal cortex, and increased CSF tau protein levels, ie total tau (t-tau)and phosphorylated tau (p-tau) [Mak H.K, Zhang Z, Yau K.K, Zhang L, Chan Q, Chu L.W]. Quantitative volumetric brain MRI can differentiate AD from healthy elderly persons, with over 80% accuracy [Scheltens P, Leys D, Barkhof F]. Semi-quantitative visual hippocampal assessment categorises hippocampal atrophy into five grades, and is also helpful with its diagnostic sensitivity of 81% and specificity of 67% [Tartaglia M.C, Rosen H.J, Miller B.L].Functional imaging by PET or single photon emission computed tomography (SPECT) can evaluate brain function. [^{18}F]FDG PET is used to measure the brain metabolic energy, while 99mTc hexa methyl propyleneamine oxime is commonly used to study cerebral perfusion.

4.2.1 The role of biomarkers for diagnosing AD

In AD patients, the characteristic change in FDG PET brain scans is bilateral hypometabolism of the superior posterior temporal and parietal lobes. In very early or mild cognitive impairment due to underlying AD pathology, FDG PET brain scans reveal hypometabolism in the medial part of the parietal cortex (posterior cingulate). In advanced AD, bilateral frontal lobe hypometabolism is also present, in addition to the characteristic hypometabolism of the temporoparietal areas (Fig 2). The sensitivity and specificity of FDG PET brain scans in the diagnosis of AD are 93% and 63%, respectively. Although SPECT brain scan is less sensitive than FDG PET, it can demonstrate the temporoparietal and posterior cingulate hypoperfusion in AD patients. The sensitivity and specificity of SPECT brain scan for the diagnosis of AD are 63% and 93%, respectively. Amyloid PET brain scans can detect Aβ deposit in the brain of AD patients in vivo. The most extensively reported technique is the [^{11}C]PiB PET brain scan. In AD patients but not in cognitively normal elderly persons, PiB is deposited bilaterally in the frontal, parietal, temporal, and occipital cortices (Fig 3). This pattern concurs with Aβ deposits in post-mortem brain studies. In the presence of dementia, a positive PiB PET brain scan confirms the diagnosis of AD as the cause [Quigley H, Colloby S.J, O'Brien J.T]. However, a positive PiB PET brain scan can also be found in 10 to 30% of cognitively normal elderly persons. This is not surprising, as amyloid deposits have been reported in autopsied brains of elderly persons without dementia,which may represent a pre-clinical stage of AD at a time when the cognitive function is still unimpaired [Villemagne V.L, Pike K.E, Darby D]. In previous studies, it was found that elderly persons without dementia but high PiB positive scans have increased risks of cognitive decline and developing AD on follow-up [Morris J.C, Roe C.M, Grant E.A, Sperling R.A, Aisen P.S, Beckett L.A]. Brain scans using PiB PET and MRI are reported to be complementary in providing neuropathological and neuronal degeneration information, respectively [Fjell A.M, Walhovd K.B, Fennema-Notestine C]. A low CSF Aβ42 level is an alternative evidence of amyloid deposition which supports the diagnosis of AD. High CSF levels of t-tau or p-tau indicate neuronal degeneration and also support the diagnosis [de Souza L.C, Chupin M, Lamari F, Mattsson N, Zetterberg H, Hansson O] The combination of CSF Aβ42 and t-tau or p-tau (ie the ratio of either t-tau/Aβ42 or p-tau/Aβ42) has a higher sensitivity and specificity than either tau or Aβ42 alone in differentiating AD from normal or other neurological diagnoses. The p-tau/ Aβ42 ratio is the best CSF biomarker to differentiate AD from frontotemporal dementia and semantic dementia, with a sensitivity of approximately 92% and 98%, respectively, and a specificity of approximately 93% and 84%, respectively. In patients with mild cognitive impairment, the combination of t-tau and the p-tau/Aβ42 ratio can also predict subsequent

development of AD, with a sensitivity of 83 to 95% and a specificity of 87 to 88% [Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L, Thompson P.M., Hayashi K.M., de Zubicaray G.I].

4.3 Neuroimaging techniques

Neuroimaging is being increasingly used to complement clinical assessments in the early detection of Alzheimer's disease (AD). Structural magnetic resonance imaging (MRI) and metabolic positron emission tomography (FDG-PET) are the most clinically used and promising modalities to detect brain abnormalities in individuals who might be at risk for AD but who have not yet developed symptoms. In the nearly 30 years that neuroimaging has been applied to the study of AD, several important discoveries have been made. Primary has been the detection of the brain signature of AD relative to normal elderly controls, followed by the differential diagnosis of AD from other neurodegenerative diseases, and finally longitudinal imaging studies of disease progression [Convit A., de Leon M.J., Tarshish C]. The goal of the early MRI and FDG-PET studies in AD was to identify general evidence for brain damage that was specifically associated with AD and with the severity of the clinical symptoms. MRI studies in AD patients have shown that cortical atrophy occurs in defined sequences as the disease progresses, comparable to the pattern of NFT accumulation observed in cross section at autopsy. Most MRI studies show that severe entorhinal cortex and hippocampal atrophy is consistently found in mild AD patients [de Toledo-Morrell, L., Sullivan, M.P., Morrell, Jack Jr., C.R., Petersen, R.C., O'Brien, P.C, Bobinski, M., de Leon M.J., Convit A], whereas volume reductions in the cortical regions, particularly parieto-temporal, posterior cingulate/ precuneus, and frontal cortices, become apparent in moderate to severe AD There is evidence that the volume loss detected on MRI is related to both the extent of NFT pathology and to the magnitude of neuronal loss [Bobinski M., de Leon M.J., Wegiel J]. As neuronal degeneration and the formation of insoluble amyloid deposits and neuritic tangles gradually progress, AD pathology is known to have the general effect of disrupting axonal transport and inducing widespread metabolic declines. On FDG-PET examinations, AD patients present with severe reductions in the rate of brain glucose consumption as compared to normal, which reflects decreased synaptic functioning and density. Virtually all FDG-PET studies report that, as compared to age-matched healthy normal controls, AD patients show regional metabolic reductions involving the parieto-temporal and posterior cingulate cortices, and the frontal areas in advanced disease. These regional metabolic reductions are present upon a background of widespread global metabolic impairment and in comparison to the relatively spared primary motor

and visual areas, cerebellum, thalamus and basal ganglia nuclei. With increasing technical improvements leading to high spatial resolution scanners and improved detector sensitivity of PET instrumentation, there also appeared reports of hippocampal metabolic abnormalities in AD along with the typical cortical hypometabolism. These findings have been largely replicated since the early 1980's, and this pattern of hypometabolism is now accepted as a reliable in vivo hallmark of AD, because of its high sensitivity in distinguishing AD from normal aging as well as from other diseases that affect the brain regionally and globally. MRI exams are now routinely requested during the clinical work-up diagnosis. After clinical examinations and routine laboratory tests are completed, the physician usually orders a structural imaging examination, i.e. CT or MR scan of the brain. Such images are recommended and used to rule out other possible common causes of dementia, such as brain tumor, normal pressure hydroencephalus, and vascular lesions FDG-PET has been recently approved by the Centers for Medicare & Medicaid Services (CMS, USA) as a routine examination tool in support of the clinical and differential diagnosis of AD. The hope is that neuroimaging evaluations would improve the detection of AD at very early stages [Mazziotta J.C., Phelps M.E].

4.4 Databases for early diagnosis

The Alzheimer's disease Neuroimaging Initiative (ADNI) and Open Access Series of Imaging Studies (OASIS) are the two most important organizations for collecting the databases related for diagnosing AD.

4.4.1 ADNI

The Alzheimer's disease Neuroimaging Initiative (ADNI) unites researchers with study data as they work to define the progression of Alzheimer's disease. ADNI researchers collect, validate and utilize data such as MRI and PET images, genetics, cognitive tests, CSF and blood biomarkers as predictors for the disease. Data from the North American ADNI's study participants, including Alzheimer's disease patients, mild cognitive impairment subjects and elderly controls. Alzheimer's disease (AD) affects almost 50% of those over the age of 85 and is the sixth leading cause of death in the US. Since 2005, the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) has been validating the use of biomarkers including blood tests, tests of cerebrospinal fluid, and MRI/ PET imaging for Alzheimer's disease (AD) clinical trials and diagnosis.ADNI also maintains an unprecedented data access policy intended to encourage new investigation and to increase the pace

of discovery in the race to prevent, treat, and one day cure AD. All data is made available without embargo.

Armed with better knowledge of the first indications of AD from ADNI and other studies, researchers are beginning to test potential therapies at the earliest stages feasible when there may the greatest promise for slowing down progression of this devastating disease. ADNI is a global research effort that actively supports the investigation and development of treatments that slow or stop the progression of AD. This multisite, longitudinal study assesses clinical, imaging, genetic and biospecimen biomarkers through the process of normal aging to early mild cognitive impairment (EMCI), to late mild cognitive impairment (LMCI), to dementia or AD. With established, standardized methods for imaging and biomarker collection and analysis, ADNI facilitates a way for scientists to conduct cohesive research and share compatible data with other researchers around the world.

4.4.1.1 ADNI phases

The ADNI study has three phases: ADNI1, ADNI GO and ADNI2. New participants were recruited across North America during each phase of the study and agreed to complete a variety of imaging and clinical assessments. Participants are followed and reassessed over time to track the pathology of the disease as it progresses. ADNI or ADNI1 is a non-randomized natural history non-treatment study in which a total of 800 subjects including 200 normal controls, 400 individuals with MCI, and 200 subjects with mild AD will be recruited at approximately 50 sites in the United States and Canada for longitudinal follow up. ADNI GO is a non-randomized natural history non-treatment study in which 200 newly enrolled subjects from approximately 50 sites from the United States and Canada and approximately 450-500 subjects will be followed from the original ADNI study. ADNI2 is also a non-randomized natural history non-treatment study where 550 newly enrolled subjects (150 CN, 100 EMCI, 150 LMCI, 150 mild AD) from approximately 55 sites from the United States and Canada, approximately 450-500 CN and LMCI subjects will be followed from the original ADNI study and approximately 200 EMCI subjects will be followed from the ADNI-GO study [www.adni-info.org].

4.4.2 OASIS

The Open Access Series of Imaging Studies (OASIS) is a project aimed at making MRI data sets of the brain freely available to the scientific community. By compiling and freely distributing MRI data sets, we hope to facilitate future discoveries in basic and clinical neuroscience. OASIS is

made available by the Washington University Alzheimer's Disease Research Center, Dr. Randy Buckner at the Howard Hughes Medical Institute (HHMI) at Harvard University, the Neuroinformatics Research Group (NRG) at Washington University School of Medicine, and the Biomedical Informatics Research Network (BIRN).The dataset can be classified into two: First one is the Cross-sectional MRI Data in Young, Middle Aged, Nondemented and Demented Older Adults which consists of a cross-sectional collection of 416 subjects aged 18 to 96. For each subject, 3 or 4 individual T1-weighted MRI scans obtained in single scan sessions are included. The subjects are all right-handed and include both men and women. 100 of the included subjects over the age of 60 have been clinically diagnosed with very mild to moderate Alzheimer's disease (AD). Additionally, a reliability data set is included containing 20 nondemented subjects imaged on a subsequent visit within 90 days of their initial session. Second one is based on the Longitudinal MRI Data in Nondemented and Demented Older Adults which consists of a collection of 150 subjects aged 60 to 96. Each subject was scanned on two or more visits, separated by at least one year for a total of 373 imaging sessions. For each subject, 3 or 4 individual T1-weighted MRI scans obtained in single scan sessions are included. The subjects are all right-handed and include both men and women. 72 of the subjects were characterized as nondemented throughout the study. 64 of the included subjects were characterized as demented at the time of their initial visits and remained so for subsequent scans, including 51 individuals with mild to moderate Alzheimer's disease. Another 14 subjects were characterized as nondemented at the time of their initial visit and were subsequently characterized as demented at a later visit. For each subject, a number of images are provided, including: 1) 3-4 images corresponding to multiple repetitions of the same structural protocol within a single session to increase signal-to-noise, 2) an average image that is a motion-corrected coregistered average of all available data, 3) a gain-field corrected atlas-registered image 4) a masked version of the atlas-registered image in which all non-brain voxels have been assigned an intensity value of 0, and 5) a grey/white/CSF segmented image [www.oasis-brains.org].

5. Recent advances in AD research

Current diagnosis of Alzheimer's relies largely on documenting mental decline. Researchers hope to discover an easy and accurate way to detect Alzheimer's before these devastating symptoms begin. Experts believe that biomarkers offer one of the most promising paths. Biomarkers are reliable predictors and indicators of a disease process. Biomarkers include proteins in blood or spinal fluid, genetic variations (mutations) or brain changes detectable by imaging. Researchers are also investigating whether presymptomatic Alzheimer's disease causes consistent, measurable

changes in urine or blood levels of tau, beta-amyloid or other biomarkers. In addition, scientists are exploring whether early Alzheimer's leads to detectable changes elsewhere in the body. For example, Lee Goldstein, MD, PhD has been funded by the Alzheimer's Association to investigate whether beta-amyloid forms characteristic deposits in the lens of the eye. Neuroimaging is among the most promising areas of research focused on early detection. Today, a standard workup for Alzheimer's disease often includes structural imaging with magnetic resonance imaging (MRI) or computed tomography (CT). These tests are currently used chiefly to rule out other conditions that may cause symptoms similar to Alzheimer's but require different treatment. Structural imaging can reveal tumors, evidence of small or large strokes, and damage from severe head trauma or a buildup of fluid in the brain. Preliminary research suggests that emerging imaging technologies and new applications of current technology may be able to detect hallmark changes associated with Alzheimer's disease in the brains of living individuals. If further research confirms the potential value of brain imaging, its use may one day be expanded to play a more direct role in diagnosing Alzheimer's and in earlier detection of the disease. Structural imaging studies have shown that the brains of people with Alzheimer's shrink significantly as the disease progresses. Research has also shown that shrinkage in specific brain regions such as the hippocampus may be an early sign of Alzheimer's. However, scientists have not yet agreed upon standardized values for brain volume that would establish the significance of a specific amount of shrinkage for any individual person at a single point in time. Functional imaging research with positron emission tomography (PET) and other methods suggests that those with Alzheimer's typically have reduced brain cell activity in certain regions. For example, studies with fluorodeoxyglucose (FDG)-PET indicate that Alzheimer's disease is often associated with reduced use of glucose (sugar) in brain areas important in memory, learning and problem solving. However, as with the shrinkage detected by structural imaging, there is not yet enough information to translate these general patterns of reduced activity into diagnostic information about individuals. Molecular imaging technologies are among the most active areas of research aimed at finding new approaches to diagnose Alzheimer's in its earliest stages. Molecular strategies may detect biological clues indicating Alzheimer's is under way before the disease changes the brain's structure or function, or takes an irreversible toll on memory, thinking and reasoning. Molecular imaging compounds currently used in Alzheimer research include:Pittsburgh compound B (PIB) and18F flutemetamol (flute**)**.The Alzheimer's Association helped fund early PIB development. The Association in 2006 also awarded a $2.1 million grant to the Researchers are also investigating whether presymptomatic AD causes consistent, measurable changes in urine or blood levels of tau, amyloid-β or other biomarkers [www.alz.org].

6. Discussion

Even though there are different neuropathology related tests, various imaging modalities, biomarkers and drug therapies etc for the diagnosis of AD, they are insufficient for a definite diagnosis. But if we can combine the features of all of the above using soft computing techniques such as fuzzy logic, neural computing, evolutionary computation and probabilistic reasoning, it may be possible to early diagnosis of the disease in a convenient way. Soft computing differs from conventional (hard) computing in that, unlike hard computing, it is tolerant of imprecision, uncertainty, partial truth and approximation. In effect, the role model for soft computing is the human mind. The guiding principle of soft computing is: "Exploit the tolerance for imprecision, uncertainty, partial truth, and approximation to achieve tractability, robustness and low solution cost". The clinical data may consists of missing , incorrect and sometimes incomplete values set so using soft computing is the better alternative to handle such data. The principal constituent methodologies in soft computing are complementary rather than competitive. Fuzzy logic handles imprecision, neural computing deals with learning, evolutionary computation is for optimization and probabilistic reasoning handles uncertainty.

7. Conclusion

There are a lot of clinical tests, drug therapies and diagnostic tools such as biomarkers and neuroimaging techniques are available for the diagnosis of Alzheimer's disease. But the fact is that these techniques are inadequate for the definite diagnosis at the earlier stages. So a newly reliable and efficient method should be developed in order to diagnose the disease with the advanced Biomedical Engineering technology using the aid of various clinical tests, neuroimaging techniques such as SPECT, MRI, PET etc, databases such as ADNI, OASIS etc and soft computing tools. With the help of above methods profiling of human body parameters for diagnosing AD can be made. The screening tests for identifying the AD patients early can be conducted with minimum effort. A clinical follow up for carry out the diagnosis can be set with the above approaches. The AD conformation test can be made with minimum cost and time. As the AD can be classified as mild, moderate and severe stages, identification of these stages is a difficult task. The early identification of these stages can be made with the above mentioned methods in a reliable and effective way. As we know that this disease is progressing worldwide with no suitable diagnosis, an effective approach towards this can be made with a point of view to diagnose AD with the minimum effort, cost and time.

References

1. Sandeep C.S, Sukesh Kumar.A, "A Review Paper on the Databases Used for the Early Diagnosis of Alzheimer's Disease(AD)", in proceedings of the International Conference on Intelligent Engineering Systems , EASA College of Engineering, Coimbatore, India, ISBN 978-93-83459-33-9, Apr 2014, p.145
2. Sandeep C.S, Sukesh Kumar.A, "A Review Paper on the Early Diagnosis of Alzheimer's Disease(AD) through Profiling of Human Body Parameters", Scientistlink, Coimbatore, India, 2013, International Journal of Computer Science and Engineering Communications (IJCSEC), Vol.1 Issue.1, pp. 21-29, December 2013.
3. 2010 Alzheimer's Disease Facts and Figures. Rep. Vol. 6. Chicago: Alzheimer's Association, 2010. Print. Alzheimer's and Dementia.
4. Alzheimer A. "Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde", Neurologisches Centralblat, 1906; 23: 1129–36.
5. Alzheimer's Disease International, World Alzheimer Report 2011, "The benefits of early diagnosis and intervention," by Prof Martin Prince, Dr Renata Bryce and Dr Cleusa Ferri, Institute of Psychiatry, King's College London, Summary, p.4.
6. ADI press release (http://www.alz.co.uk/media/nr100921.html) for "Alzheimer's Disease International World Alzheimer Report 2010: The Global Economic Impact of Dementia," Prof Anders Wimo, Karolinska Institutet, Stockholm, Sweden Prof Martin Prince, Institute of Psychiatry, King's College London, UK. Published by Alzheimer's Disease International (ADI) 21 September 2010.
7. Shimokawa et al., "Influence of deteriorating ability of emotional comprehension on interpersonal behavior in Alzheimer-type dementia", Brain and Cognition 47(3): pp. 423–433, 2001.
8. AA, 2012. Alzheimer's Facts and Figures. Alzheimer's Association.
9. WAD, 2011. World Alzheimer's Day on Wednesday.
10. Frosch, M.P., D.C. Anthony and U.D. Girolami, 2010. The Central Nervous System. In: Robbins and Cotran Pathologic Basis of Disease, Robbins, S.L., V. Kumar, A.K. Abbas, R.S. Cotran and N. Fausto (Eds.), Elsevier srl, Philadelphia, ISBN-10: 1416031219, pp: 1313-1317.
11. Harvey, R.A., P.C. Champe, B.D. Fisher, Lippincott's Illustrated Reviews: Microbiology. 2nd Edn., Lippincott Williams and Wilkins, ISBN-10: 0781782155,pp: 432, 2006.

12. Cummings, J.L., H.V. Vinters, G.M. Cole and Z.S. Khachaturian, Alzheimer's disease: etiologies, pathophysiology, cognitive reserve and treatment opportunities. Neurology. 51: 2-17. PMID: 9674758, 1998.
13. Yaari, R. and J. Corey-Bloom, Alzheimer's disease: Pathology and pathophysiology. Semin Neurol. 27: 32-41, 2007.
14. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med; 144:73-81, 2006.
15. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci; 26:81-104, 2003.
16. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry; 74:1206-9, 2003.
17. Sukesh Kumar.A, Jyothiraj V.P, Subin T.K, "Automated diagnosis system for temporal bone abnormalities**",** AMSE Journals, Modelling measurement and control, Series C, vol. 70, No 1-2, 2009.
18. Sheeba.O, Sukesh Kumar.A, "Image enhancement and histogram equalization in the detection of drusen deposit in human retina**",** AMSE Journals, Modelling measurement and control, Series C, vol. 71, No 1-2, 2010.
19. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet; 366:2112-7, 2005.
20. Chiu HF, Lam LC, Chi I, et al. Prevalence of dementia in Chinese elderly in Hong Kong. Neurology; 50:1002-9, 1998
21. Hy LX, Keller DM. Prevalence of AD among whites: a summary by levels of severity. Neurology; 55:198-204, 2000.
22. Chu LW, Tam S, Wong RL, et al. Bioavailable testosterone predicts a lower risk of Alzheimer's disease in older men. J Alzheimers Dis; 21:1335-45, 2010.
23. Chan KK, Chiu KC, Chu LW. Association between alcohol consumption and cognitive impairment in Southern Chinese older adults. Int J Geriatr Psychiatry; 25:1272-9, 2010.
24. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA; 302:627-37, 2009.
25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology; 34:939-44, 1984.

26. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
27. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement; 7:263-9, 2011.
28. Mak HK, Zhang Z, Yau KK, Zhang L, Chan Q, Chu LW. Efficacy of voxel-based morphometry with DARTEL and standard registration as imaging biomarkers in Alzheimer's disease patients and cognitively normal older adults at 3.0 Tesla MR imaging. J Alzheimers Dis; 23:655-64, 2011.
29. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry; 55:967-72, 1992.
30. Tartaglia MC, Rosen HJ, Miller BL. Neuroimaging in dementia. Neurotherapeutics; 8:82-92, 2011.
31. Quigley H, Colloby SJ, O'Brien JT. PET imaging of brain amyloid in dementia: a review. Int J Geriatr Psychiatry; 26:991-9, 2011.
32. Villemagne VL, Pike KE, Darby D, et al. Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. Neuropsychologia; 46:1688-97, 2008.
33. Morris JC, Roe CM, Grant EA, et al. Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. Arch Neurol 2009; 66:1469-75.
34. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease Alzheimers Dement;7:280-92, 2011.
35. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease. J Neurosci; 30:2088-101, 2010.
36. de Souza LC, Chupin M, Lamari F, et al. CSF tau markers are correlated with hippocampal volume in Alzheimer's disease. Neurobiol Aging. Epub 2011 Apr 11.

37. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA; 302:385-93, 2009
38. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol; 5:228-34, 2006.
39. Thompson, P.M., Hayashi, K.M., de Zubicaray, G.I., et al., Dynamics of gray matter loss in Alzheimer's disease. J. Neurosci. 23, 994–1005, 2003.
40. Convit, A., de Leon, M.J., Tarshish, C., et al., Hippocampal volume losses in minimally impaired elderly. Lancet 345, 266, 1995.
41. de Toledo-Morrell, L., Sullivan, M.P., Morrell, F., et al., Alzheimer's disease: in vivo detection of differential vulnerability of brain regions. Neurobiol. Aging 18, 463–468, 1997.
42. Jack Jr., C.R., Petersen, R.C., O'Brien, P.C., et al., MR-based hippocampal volummetry in the diagnosis of Alzheimer's disease. Neurology 42, 183–188, 1992.
43. Bobinski, M., de Leon, M.J., Convit, A., et al., MRI of entorhinal cortex in mild Alzheimer's disease. Lancet 353, 38–40, 1999.
44. Bobinski, M., de Leon, M.J., Wegiel, J., et al., The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. Neuroscience 95, 721– 725, 2000.
45. Mazziotta, J.C., Phelps, M.E., Positron emission tomography studies of the brain. In: Phelps, M.E., Mazziotta, J.C., Schelbert, H. (Eds.), Positron Emission Tomography & Autoradiography: Principles & Applications for the Brain & Heart. Raven Press, New York, pp. 493–579, 1986.
46. Visit "www.adni-info.org"
47. Visit "www.oasis-brains.org"
48. Visit "www.alz.org"