

# A Review Paper on Early Diagnosis of Alzheimer's disease (Ad) Through Profiling of Human Body Parameters

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**Abstract:** Geratology 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. In this case, the use of advanced biomedical engineering technology will definitely helpful for making diagnosis successfully. Profiling of human body parameter using computers can be utilised for the successful 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-Proton CT Scanning (SPECT). 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 and neuroimaging techniques.

**Keywords:** Alzheimer Disease (AD), neurodegeneration, MRI, SPECT, PET

## 1 INTRODUCTION

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[1]. Alzheimer's disease was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist [2]. 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[3]. The number of people with dementia will double by 2030, and more than triple by 2050[4]. 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 next stages of Alzheimer's disease (Mild and Moderate AD) are characterized by increasing cognitive deficits, and decreasing independence, culminating in the patient's complete dependence on caregivers and a complete deterioration of personality (Severe AD) [5]. Alzheimer's disease is the sixth-leading cause of death and is 70% prevalent in all cases of dementia[6]. According to another report every 71 sec, someone develops Alzheimer's disease and the rate doubles roughly every 10 years after age 65 [7]. The most well-known neuropathological hallmarks of AD are extraneuronal senile plaques and intraneuronal neurofibrillary tangles (NFTs). Neurofibrillary tangles are filamentous bundles in cytoplasm of the neurons displacing or encompassing nucleus.

In the pyramidal cells, they appear as 'flame' while in rounder cells they appear as 'globos tangles' [8]. Senile (neuritic) plaques present outside the neuron, appear as spherical bodies 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) [8,9]. Familial causes or genetic mutations involved in disease pathology include mutations on chromosomes 21, 14 and 1. Risk factors for AD are advanced age, lower intelligence, small head size, history of head trauma and female gender [10,11]

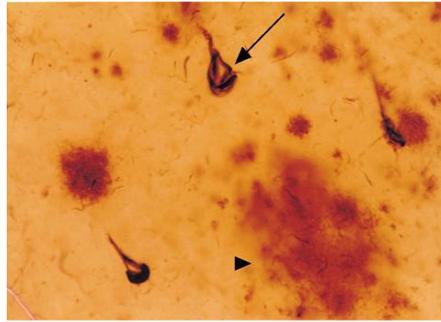
## **2 RISK FACTORS OF AD**

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 amyloid precursor protein gene on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1. Presenilin 1 gene mutations are most common among familial AD mutations[12]. Mutations in these genes lead to an overproduction of beta-amyloid (A $\beta$ ) peptides (A $\beta$ 40 and A $\beta$ 42), which give rise to synaptic dysfunction, neurotoxicity, and A $\beta$  deposits in the brain called neuritic or senile plaques. But in early-onset AD, is rare[12,13] In sporadic or late-onset AD, the apolipoprotein-E (APOE)  $\epsilon$ 4 allele increases the risk of developing the disease[12]. As a susceptibility gene, the genotypes APOE  $\epsilon$ 2/ $\epsilon$ 4 or  $\epsilon$ 3/ $\epsilon$ 4 increase the risk by approximately three-fold, and the genotype APOE  $\epsilon$ 4/ $\epsilon$ 4 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[12,14].The APOE allelic variants may be involved in the degradation or clearance of A $\beta$  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[15].

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 [12,16,17,18]. In men, high bioavailable testosterone levels appear to reduce the risk of AD[19]. Education may increase the 'cognitive reserve', which reduces the risk of late-life dementia. 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[12]. 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[12,20]. Physical activity and exercise reduce brain tissue loss, dementia, and the risk of AD, possibly via increased neurotrophic factors[21]. Smoking increases the risk 2 to 4 times. Depressive mood and cardiovascular risk factors are also associated with an increased risk[12]. Severe head injury also increases the risk of AD, possibly via reduced brain reserve or increases in brain A $\beta$  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[12,22]. 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. Plaques and tangles are found predominantly in the frontal and temporal lobes, including the hippocampus. In more advanced cases, the pathology extends to other regions of the cortex, including the parietal and occipital lobes. Plaques are insoluble extracellular deposits composed mainly of a 40–43 amino acid peptide called  $\beta$ -amyloid (A $\beta$ ). A $\beta$  derives from a larger protein,  $\beta$ -amyloid precursor protein (APP) by proteolytic processing. Plaques can be described as diffuse or classical. Diffuse plaques are amorphous aggregates of A $\beta$  which are typically not associated with dystrophic neurons and abnormal neurites. Classical neuritic plaques contain densely aggregated A $\beta$  and are generally associated with degeneration and neuronal cell loss. Because soluble  $\beta$ -amyloid aggregates spontaneously into fibrils that are indistinguishable from those found in vivo, it is thought that plaques result from raised A $\beta$  levels. 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 A $\beta$  is formed.



**Fig1:** Light micrograph of Alzheimer disease neuropathology. 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  $\beta$ -amyloid ( $A\beta$ ).

In late-onset AD, there is reduced clearance of the usual amounts of  $A\beta$ . The excess  $A\beta$  aggregates to form soluble dimers, trimers, and low-ordered molecules called oligomers. Further aggregations into  $A\beta$  protofibrils, fibrils and neuritic plaques may also occur. While all these forms of  $A\beta$  aggregates account for neuronal dysfunction and neuronal death in AD,  $A\beta$  oligomers are particularly toxic to the neuron. In AD, the second neuropathological hallmark is an intraneuronal accumulation of abnormally hyperphosphorylated tau ( $\tau$ ) (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 ( $\tau$ ) 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

Although the role of plaques and tangles in Alzheimer disease 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, parietooccipital cortex, temporal cortex and frontal 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 greatest concentration of plaques and tangles. This finding corresponds to the early and progressive symptoms of memory loss in patients with Alzheimer disease. 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 decreased 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 Alzheimer disease.

#### 4 EARLY DIAGNOSIS OF AD

While much has been accomplished in Alzheimer disease research in the last 20 years, a great deal remains to be done to improve its diagnosis and treatment. There is increasing evidence that early diagnosis of Alzheimer disease will be key to maximizing treatment benefits. But too often, patients are diagnosed in later stages of the disease, when disabling symptoms and neuropathologic 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. However, early diagnosis remains difficult to achieve, and currently the clinical diagnosis of AD comes relatively late into the disease. The difficulties lie for the most part in the similarities between cognitive impairment due to normal aging processes and initial manifestations 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. While the clinical signs of AD are well established, the early symptomatic and prodementia stage remains to be better defined.

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 [23]. 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. Less common causes of dementia are hypothyroidism, neurosyphilis, and sedation from drugs. If the clinical history raises suspicions, chronic heavy metal intoxication (eg mercury), human immunodeficiency virus infection, and Creutzfeldt-Jakob disease have to be considered. Overall, AD accounts for 65% of all patients with dementia, while secondary causes explain a minority [17]. 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[23,24]. 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 made at postmortem. 20 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).

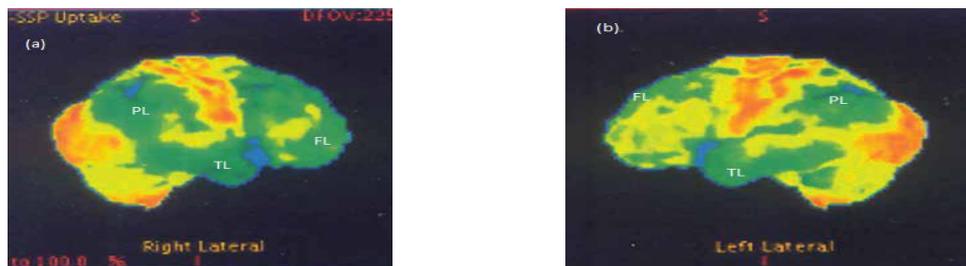
#### **4.1 BIOMARKERS OF AD**

Alzheimer's disease is now regarded as a chronic 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) A $\beta$ 42 levels constitute neuropathological biomarkers, reflecting A $\beta$  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)[25]. Quantitative volumetric brain MRI can differentiate AD from healthy elderly persons, with over 80% accuracy[26]. 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% [27]. 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  $^{99m}$ Tc hexamethyl propyleneamine oxime is commonly used to study cerebral perfusion. 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[28]. Amyloid PET brain scans can detect A $\beta$  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 A $\beta$  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[28,29]. 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 [29]. 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[30,31,32]. Brain scans using PiB PET and MRI are reported to be complementary in providing neuropathological and neuronal degeneration information, respectively [32]. A low CSF A $\beta$ 42 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[25,33]. The combination of CSF A $\beta$ 42 and t-tau or p-tau (ie the ratio of either t-tau/A $\beta$ 42 or p-tau/A $\beta$ 42) has a higher sensitivity and specificity than either tau or A $\beta$ 42 alone in differentiating AD from normal or other neurological diagnoses.

The p-tau/ A $\beta$ 42 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[34]. In patients with mild cognitive impairment, the combination of t-tau and the p-tau/A $\beta$ 42 ratio can also predict subsequent development of AD, with a sensitivity of 83 to 95% and a specificity of 87 to 88%[35,36].

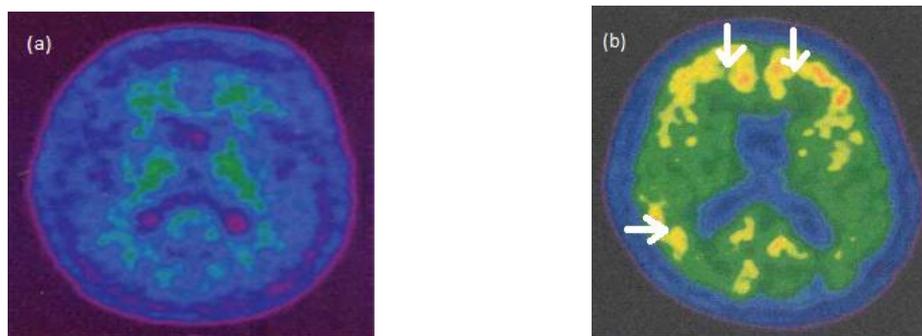
#### 4.2 NEUROIMAGING TECHNIQUES

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. 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.



**FIG 2.** Fluorodeoxyglucose positron emission tomography (FDG PET) brain scan in Alzheimer's disease (AD) Brain FDG PET scan in moderately severe AD: bilateral symmetrical hypometabolism affecting temporal (TL), parietal (PL), and frontal (FL) lobes

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[37]. Most MRI studies show that severe entorhinal cortex and hippocampal atrophy is consistently found in mild AD patients[38,39,40]



**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 cortices

Whereas volume reductions in the cortical regions, particularly parieto-temporal, posterior cingulate/presumes, 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 [41,42]. 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[43]. 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 hydrocephalus, 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.

## **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 tumours, evidence of small or large strokes, and damage from severe head trauma or a build-up 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) and <sup>18</sup>F 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- $\beta$  or other biomarkers.

## **6 CONCLUSION**

There are a lot of clinical tests, drug therapies and diagnostic tools such as biomarkers and neuroimaging techniques 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 and PET. These techniques can be useful to a great extent for the profiling of human body parameters which are the main hallmarks of the disease.

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