The Early Diagnosis of Alzheimer's Disease (AD) Using CAMD, TREAD and NAAC Databases

Sandeep C S[1], Sukesh Kumar A[2],Susanth M J[3]
[1, 2, 3]Department of Electronics & Communication Engineering
[1, 2] Faculty of Engineering, University of Kerala, Trivandrum, India
[3]Consultant Neurologist, SUT Hospital, Trivandrum, India

Abstract-*Alzheimer Disease (AD) is one of the common forms of dementia which is an irreversible neurodegenerative progressive disorder of the brain which affects the elderly population above the age of 65. Alzheimer is a brain disease that causes problems with memory, thinking and behaviour. It is severe enough to interfere with daily activities. Alzheimer symptoms are characterized by memory loss that affects day-to-day function, difficulty performing familiar tasks, problems with language, disorientation of time and place, poor or decreased judgment, problems with abstract thinking, misplacing things, changes in mood and behaviour, changes in personality and loss of initiative. There are different types of tests associated with AD such as neuropsychological tests, laboratory tests and various imaging modalities for the early diagnosis of AD. Although these tests are available, they are inadequate for the definite diagnosis of the disease. In this paper we focus on the databases related to AD such as CAMD (Coalition Against Major Diseases), NAAC(National Alzheimer's Coordinating Center) and TREAD (Trajectory-Related Early Alzheimer's Database). The use of these databases, soft computing techniques and image analysis from the different imaging modalities in an efficient way for making a definite diagnosis and early prediction of AD. Our aim is to predict the early diagnosis in a reliable manner such that to combine the values of different tests with the help of soft computing techniques to develop software tool for a definite diagnosis.*

Keywords-Alzheimer Disease, Dementia, CAMD, TREAD, NAAC, Soft Computing techniques, image analysis.

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive deteriorating and loss function of the neurons in the human brain. It leads to loss of memory of the subject and weakens the proficiency in doing a sequence of actions regularly following [1, 2]. AD is the sixth-leading cause of death among various diseases and is 70% widespread in all cases of dementia [3]. According to another report every 71 sec, someone develops Alzheimer's disease and the rate doubles roughly every 10 years after age 65 [4]. Some studies show that almost 36 million people are believed to be living with Alzheimer's disease and other types of dementias. This will increase to about 66 million by 2030 and nearly 115 million by 2050[5]. The development of AD can be placed into four stages. The first stage is called Mild Cognitive Impairment (MCI) that does not make prominent changes in day to day living. The second and third stages of the disease are called as Mild and Moderate AD. These stages describe the distinctive nature by a rise in cognitive shortfall, and reduction in independence. The fourth stage is called Severe AD in which the affected person almost dependent on caregivers and an overall decline of personality [6]. Alzheimer's disease is one of the underlying causes of dementia, the term used to point out weakened brain functions and related symptoms like difficulty in performing routine tasks, memory loss, confusion, loss of intellectual functions and poor judgment. The above mentioned conditions are similar symptoms of below mentioned neurological disarrays. This includes Alzheimer's disease, Frontotemporal Dementia , vascular dementia, Dementia with Lewy Bodies, Normal-Pressure Hydrocephalus , Parkinson's disease, and Delirium or Depression. AD is the most common type of dementia and is clinically evident when there is gradual loss of brain functions. The symptoms thus occurring may lead to disorientation and aphasia (difficulty in language), indicating cortical dysfunction, agnosia (impairment in recognizing object and people), apraxia (impaired motor function) and significant of all, memory impairment. As the disease develops drastically, the patients suffer disability and immobility. The brain of such patients shows gross cortical atrophy with ventricular enlargement.

The most widely known neuropathological hallmarks of AD are extraneuronal senile plaques which are seen outside the neuron and intraneuronal neurofibrillary tangles that are seen inside the neuron. 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' [7]. Senile 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) [7, 8]. Familial causes or genetic reasons involved in disease

pathology include mutations on chromosomes 21, 14 and 1. Risk factors for AD are elder age, small head size, history of head trauma, lower intelligence, and female gender [9, 10]. The imaging modalities tests that were established for AD are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography and neuropsychological tests. CT scans were used to check for structural deterioration of the brain and increased ventricle size. It was noticed that at firstly cerebral atrophy was predominant in AD patients than control subject. However it was discovered later that healthy people also have cerebral atrophy. Patients with dementia may not have cerebral atrophy at least in the early stages of the disease. From these findings it was difficult to distinguish between a healthy elderly patient and a patient with dementia. So the CT scans have been deemed as clinically not as useful in the primary diagnosis of AD. After CT structural MRI was introduced to evaluate MCI (mild cognitive impairment) to AD in addition to clinical measures. Structural MRI measures the whole brain volumes, medial temporal lobe structures, and ventricular volumes. Therefore MRI can be helpful in differentiating between MCI and AD [11]. PET is an imaging modality that uses biochemical ways of getting images rather than structural information. Alzheimer's disease is one of the underlying causes of dementia. Dementia is the term used to indicate impaired brain functions and encompass symptoms like memory loss, confusion, difficulty in performing routine tasks, loss of intellectual functions and impaired judgment. PET technology includes the detection of photons which records the levels of radioactivity beginning from given points in time and space. Positron emitting radioisotopes are used to generate the radioactivity [13]. PET scan measures different compounds in the brain especially the fluorodeoxyglucose (FDG) that can compete with glucose for metabolism and absorption in neurons. With AD the neurons intake of glucose and FDG becomes less. By projecting the regions of decreased FDG uptake, PET can help in the early diagnosis of AD, even in the absence of the gross structural damage detected by other imaging techniques such as CT or magnetic resonance imaging [12].Some studies have been conducted to examine patients that are deemed amyloid positive or amyloid negative, PET has been used extensively to study AD, and it is evolving into an effective tool for early diagnosis. PET is a very costly scan to perform the test for AD, it has been the most useful to provide visual images in the detection of the disease. There are some recent advances in technology that can not only detect AD, but it can possibly explain the symptoms and how the disease works.

The neuropsychological tests are used to examine the specific type and level of cognitive impairment that the patient is having. Some of them that were, " Mini Mental State Examination, Trial Making Test parts A and B, Digit Symbol Substitution Test, Digit Span forward and backward, Rey Auditory Verbal Learning Test, category fluency, and the Clock Drawing task" [13]. All of these tests are helpful in showing the memory recall of a patient and the realizable areas where the patient may degrade. Using the above different tests, it can be helpful to determine the types of treatment plans which are to be used. However neuropsychological tests alone are not helpful in detecting early AD, trials were often conducted combining neuropsychological tests with clinical tests and various imaging modalities. 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 have conducted a review on the different databases such as TREAD, CAMD and NAAC for determining the sensitive disease progression changes in the affecting areas related to Alzheimer's disease. By these online databases and other data obtain from hospitals, clinical trials and different tests we can develop an expert system help of image analysis and soft computing techniques.

II. COALITION AGAINST MAJOR DISEASES (CAMD) ALZHEIMER'S DISEASE DATABASE

The Critical Path Institute (C-Path), in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution, has formed the Coalition Against Major Diseases (CAMD).The team members consists of 6 non profit groups representing patients' interests, fifteen leading pharmaceutical companies, and the National Institute of Neurological Disorders and Stroke (NINDS), the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), 2 institutes of the National Institutes of Health (NIH), the National Institute on Aging (NIA)and representatives from academia. The coalition's aim is to transform the drug development model for neurodegenerative irreversible diseases and serve as a paradigm for other major diseases. In 2004, the FDA's Critical Path Initiative has found neuropsychiatric diseases and disease models as most important areas of active research opportunities [14]. The work of the coalition will focus on member companies sharing of precompetitive data, which may include data from placebo groups from clinical trials. In addition, industry will contribute scientific expertise that will lead to improved knowledge across disciplines which is an important part in the development of treatments for Parkinson's and Alzheimer's diseases. Better management of recent knowledge will be aimed at qualifying for use in novel imaging or biochemical markers, drug development, and quantitative disease progression models. The CAMD will avoid using terms like "valid" or "surrogate" to describe biomarkers. Instead of

these, the CAMD will seek to find methods that are "qualified for use" based on a careful review of scientific data by scientists from academia, regulatory agencies and industry. These "qualified" methods are expected to lead to an improved efficiency in decision making during the drug development process and to a decrease in drug failures during late phase testing. The database regarding CAMD is as follows:

The database consists of 6,500 patients across 24 clinical trials of AD and MCI, but is not limited to, demographic information, APOE4 genotype, concomitant medications and cognitive scales (MMSE and ADAS-Cog). All data has been rearranged to a common data standard such that all the data can be analyzed across all studies. It is openly available to CAMD members, as well as to external qualified researchers who submit, and are approved for, a request for access; biomarker data of AD biomarkers. The real names of test drug subjects from sponsor companies and background therapies per individual case are not included in it. The Primary applications for the Alzheimer's disease C-Path Online Data Repository are characterizes the dynamics of the placebo-arm within clinical trials of AD and MCI, Serves as a tool for the development of simulation and modelling tools for AD clinical trials [14]. The data is mapped to the CDISC foundational and AD-specific Study Data Tabulation Model (SDTM). Knowledge of SDTM is required for effective use of the data. Information and training on SDTM training is available from CDISC: no SDTM training is provided within CODR. The data consists of 11 SDTM domains: Subject Characteristics (SC), Subject Visits (SV), Questionnaires (QS), Laboratory Tests (LB), Disposition (DS), Demographics (DM), Adverse Events (AE), Concomitant Medications (CM), Medical History (MH), Vital Signs (VS) and Supplemental Qualifier (SUPPQUAL). A summary of the more salient concepts captured by SDTM domains contained in the CAMD AD database is provided in the table1 below.

Domain	Contents
DM	Age Gender Race Ethnicity Country
SC	Gender
CM	Ethnicity Country*ApoE Genotype
AE	*MTHFR Genotype **Acetylcholinesterase Inhibitors**Memantine
MH	**General Medications ***Event Severity
VS	Duration Primary Diagnosis (MCI or AD) Family History of AD General Medical History SBP, DBP Heart Rate
QS	Temperature Weight, Height,BMI
LB	Respiratory Rate
*ApoE = Apolipoprotein E; MTHFR = Methylenetetrahydrofolate Reductase. **Memantine and AChEi drug names are standardized in the CMDECOD field. All other drug names are provided in the verbatim terminology supplied to CAMD.	

Table 1: CAMD database (source: c-path.org)

III. NATIONAL ALZHEIMER'S COORDINATING CENTER (NACC)

NACC serves as a repository for data collected at nearly 29 Alzheimer's Disease Centers (ADCs) throughout the United States. The ADCs conduct clinical and biomedical research on Alzheimer's disease and related disorders. Centers enrol their study participants in various ways. It includes referral from clinicians, self-referral by patients themselves or concerned family members and active recruitment through community organizations, volunteers who wish to contribute to research on various types of dementia [15,16]. Most centers also enrol volunteer control subjects. Study subjects at each center are best regarded as a case series, not necessarily representing all cases of disease in a defined population. The

three main data research sets available from NACC are summarized in the table 2 below. NACC also archives several other, more specialized data sets, as described below.

	Uniform Data Set (UDS) (LONGITUDINAL)	**Neuropathology Data Set (NP)**	**Minimum data set (MDS)**
Years covered	Sept. 2005 - present	1984 - present	1984 - 2005
Study subjects	Enrollees followed at ADCs (with or without dementia)	Subjects who died and underwent autopsy	Enrollees followed at ADCs
Approx. # of subjects*	28,444	13,279	74,397
Time period covered for each subject	Initial visit and each annual follow-up visit, plus milestones such as death or dropout	Status of brain at autopsy	Mainly status on last ADC visit; some variables also capture initial-visit status
Method of data collection	Collected by clinicians, neuropsychologists, and other ADC research personnel, using up to 18 standardized forms at each visit.	Standardized neuropathology form, completed by neuropathologist	Mainly abstracted retroactively from ADC medical records
Topics covered (brief list)	Sociodemographics on subject and informant, family history, dementia history, neurological exam findings, functional status, neuropsych-ological test results, clinical diagnosis, whether imaging testing done, ApoE genotype	Demographics, date of death, primary and secondary neuropathological diagnoses, presence/absence of neuropathological features of most major dementias, APOE genotype, brain weights	Demographics, cognitive status, clinical dementia diagnosis, selected clinical manifestations, MMSE score, vital status, primary neuropathological diagnosis

Table 2: main data research sets available from NACC (source:www.alz.washington.edu)

IV. TRAJECTORY-RELATED EARLY ALZHEIMER'S DATABASE (TREAD)

In order to get suitable volunteers for trials of promising treatments with very early Alzheimer's disease (AD), the overall aim of TREAD is to help and detect the subjects that degrade in memory. TREAD will initiate a database for recruitment into new and encouraging treatment trials.AD is increasingly common as our population ages, and a hallmark is early deteriorate in memory, which can be diagnosed earlier prior to severe memory problems using computerized memory testing. TREAD use computer tests of memory and thinking developed in Melbourne that can be done over the internet and repeated periodically to see if a person's memory is becoming worse compared to their own baseline performance. This is a very sensitive way of detecting decline in memory and to identify people who should be offered further evaluation for possible causes, one of which is Alzheimer's disease. If evaluation suggests AD as the cause, they aim to offer participation in separate trials of promising new treatment methods. Subjects in this study should have ready access to internet, and be sufficiently skilful with that computer system and can open a web browser and then follow the simple instructions of the test themselves [17]. They should also live or visit clinics in the Greater Melbourne area since they will be offered evaluation at a Melbourne clinic if decline in their memory is detected. The study will use computer tests including one developed by the Melbourne-based company CogState Ltd. The CogState test uses simple keyboard responses and playing-cards to assess speed and accuracy, which are direct measures of a person's ability to think clearly and quickly. It is designed in an easy manner to use and brief, taking about 15-20 minutes at most to complete all tasks. The practice test does not keep score; there is a scored test which would be used as the baseline for future comparisons. The test is started by clicking a web page link, runs itself interactively and when finished the results are sent to the study's secure database and analysed automatically. Initial testing would be at about monthly intervals for 6 months and then 3 monthly intervals. Most participants are likely to show no significant decline in test results, but about 10% may show decline in memory. In addition, it's possible that some subjects with symptoms or even early dementia may not decline on the tasks used in this study [17]. In addition, a

decline on the computer tests does not necessarily mean a person will get dementia or Alzheimer's disease, because there are many other possible reasons. If decline is found, it is important to consider undergoing a doctor's evaluation to seek identifiable causes of the decline. It would be your decision whether to undergo such evaluation by your own general practitioner (GP) or a Memory Clinic. The study is being conducted by the Florey Institute of Neuroscience and Mental Health (FINMH), with Principal Investigator, A/Prof David Darby, assisted by Associate Investigator Dr Amy Brodtmann. Funding is through the FINMH.

V. IMPLEMENTATION USING SOFT COMPUTING TECHNIQUES

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 constituents of soft computing are fuzzy logic, neural computing, evolutionary computation and probabilistic reasoning. 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.

VI. 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. The different database of Alzheimer disease patients discussed here gives a complete idea of how the disease can be predicted before the disease progresses and very much useful for creating computer operated software with the help of various soft computing techniques. From the above understandings it is clear that a newly reliable and efficient method should be developed in order to diagnose the disease with the advanced biomedical engineering technology techniques which can be useful to a great extent for the early and definite diagnosis of the disease.

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