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A REVIEW: ON METHODS OF DETECTION FOR ALZHEIMER'S DEMENTIA USING BIOINFORMATICS TOOLS

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Abstract

With the increase life span of humans there has been a substantial increase in the number of people being affected by the dementia disease. Yet no accurate method is known for the early diagnosis of this deadly disease. Leading techniques like MRI intensity, involvement of cells like glial and dependence of immunity on the disease have been discussed in this review to have a better understanding on various methods implemented for the prognosis of Alzheimer's Dementia (AD). A single technique cannot be used to solve the problem of domains hence, based on the complexity and the time at which the disease is diagnosed; studies suggest that which technique could be employed for the diagnosis of disease at different stages. This study can be helpful for designing a protocol which can be tailored for the medical institutions basing on the age of the patients and their condition. However, a hybrid intelligent technique could be proposed which could detect the disease in an early stage in a more effective manner.

Keywords: Alzheimer's disease, Dementia, MRI, Glial Cells, Neuro inflammation, Mild Cognitive Impairment (MCI), Amyloid β (Aβ)

1. Introduction

One of the most common forms of dementia is Alzheimer's it is a general term for memory loss and other intellectual abilities that causes enough damage to the routine life of an individual. Comparing with all the countries in the globe, India the second most populous country is facing a crisis among the aged and this crisis is being the Alzheimer's disease. Alzheimer's is independent of regular aging course in humans; although increasing age is considered as a reason of risk for most of the people with Alzheimer's as the majority of the people affected with this disease are 65 and older. Studies have revealed that approximately 5% of people have shown symptoms of Alzheimer's at an early age of 40 to 50 years. Studies have discovered the fact that Alzheimer's is a progressive disease, it's symptoms

gradually become more intense over years, at the initial stage the loss of memory is not so severe, nevertheless gradually in later stage Alzheimer's, individuals lose the ability to do routine tasks like carrying on a simple conversation and respond to their environment. Alzheimer's in India is quickly becoming a field for concern for the society, with growing life span. As of the present-day Alzheimer's has no current cure, but research is widely carried out on treatments for symptoms. Several researches have been done in this field considering various angles of the disease like comparing different magnetic strengths in MRI for the diagnosis of Alzheimer's by April J. Ho et al. [1], ALFA project by Jose Luis Molinuevo et al. [2], the involvement of the glial cells for the progression of Alzheimer's Dementia by Robert G. Nagele et al. [3] and the roles of inflammation and immnity in Alzheimer's disease by Linda J. Van Eldik et al. [4]. All these approaches have facilitated vastly in the field of diagnosis of AD (Alzheimer's Dementia).

2. Comparison of 3 T and 1.5 T MRI for Tracking Alzheimer's

One of the most widely used techniques is Magnetic resonance imaging (MRI) [5] which helps to detect various diseases including the discovery of deviations in brain volume over time. In this paper the researchers have focussed on the different magnetic strength of the MRI [6, 7] and compared them for tracking the progression of the AD. This research has used the imaging data that was assimilated from the Alzheimer's Neuroimaging Initiative (ADNI). It is a worldwide project that provides clinical data for the research of pathology principle, deterrence and cure of Alzheimer's disease (AD). It is a venture that works with alliance and support from various organisations like National Institute of Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), and several other non-profit institutions, and private pharmaceutical companies.

In the late 1990s the U.S. Food and Drug Administration approved the 3 T brain MRI for clinical use. The researchers believed that increasing the magnetic field strength from usual 1.5 T to 3 T will also increase (roughly double) the signal-to-noise ratio (SNR) and thus differentiating grey/white matter and other tissues will be done in a much more better and effective way.

The different MRI scans of 1.5 T and 3 T were acquired from several sites and time points. In the paper, 110 subjects were exposed to 1.5 T and 3 T and then they were observed over a year and the structural brain impairment was examined thoroughly. 3 and 1.5 T scans have been shown in Figure 1 for the better and easy graphical assessment. Though there are no remarkable visible alterations, the grey/white matter contrast appears to be a little greater at 3 T.

It is to be noted that this said result has been obtained from arbitrary subjects. To avoid the cohort effects the emphasis of this paper was given on the subjects with baseline and 12-month follow-up scans from both 1.5 T and 3 T. The researchers were apprehensive with the ambiguity of the inference if different set of subjects were analysed at different magnetic strength.

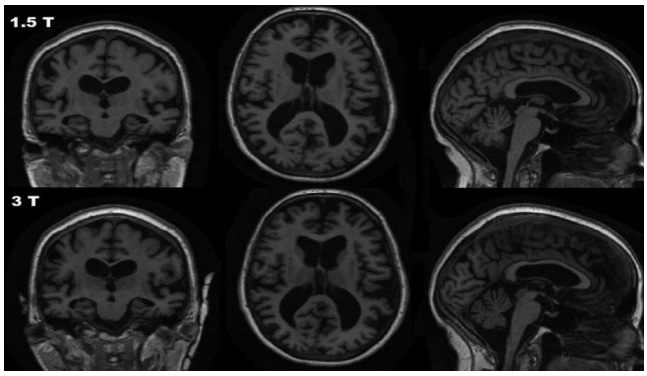

Figure 1

MRI scans of same subject: 1.5 T and 3 T, except higher spatial resolution no other striking difference is found.

The sample size was calculated per arm needed to measure a 25% slowing of the atrophic rate with 80 and 90% power to conclude whether 3 or 1.5 T MRI had more strength and was effective for the detection of the changes on the temporal lobe volume loss over 1 year. As can be seen in Figure 2, the 1.5 T MRI (n80 = 37 for AD, 108 for MCI) did not show any statistically dissimilar sample size estimate to distinguish a temporal lobe atrophy when compared to 3T (n80 = 49 for AD, 166 for MCI) in case of both the AD and MCI groups.

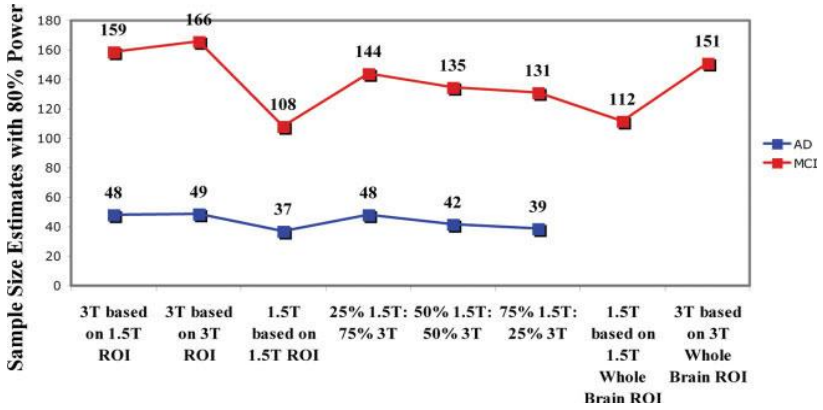

Figure 2: Sample size estimating with 80% power when mixing 1.5 T and 3T. When the 3 T scans were analysed using the 1.5 T specific statistical ROI it produced the worst performance.

3. Alfa Project [2]

For past decades researches have been going on the diagnosis of the Alzheimer's Dementia. Previous studies have elucidated that the early identification of AD can decline the economic cost for continuing the treatment of the patients by approximately 33% and also increase the life expectancy of the affected patients. After thorough

examination many *in vivo* AD biomarkers such as β-amyloid (Aβ) and tau concentration in cerebrospinal fluid (CSF) [8], hippocampal atrophy [9,10], tempo parietal hypometabolism [11,12] and cerebral amyloid deposition measured by positron emission tomography (PET [13]) were found to have extensive potential and are thus considered as key components for the diagnosis of AD. All the studies have led to the conclusion that AD pathology is a disease that slowly grows for a span of several years or even decades before the actual clinical symptoms start to appear. This stage where the disease progresses without any remarkable or visible symptoms is known as the preclinical stage of AD. A strategy should be built up for preventive studies that require the individual's identification who are at risk of acquiring AD in the near future.

With the intent of expanding our understanding of the symptoms advancing at the preclinical AD stages, which are pathogenic, the ALFA (for Alzheimer and Families) project was commenced by the Barcelona βeta Brain Research Centre (BBRC) for the group of cognitively normal subjects, most of which have their ancestors diagnosed with AD, and deals with imminent follow-up of these individuals.

This project consists of the ALFA registry, the ALFA parent cohort, and the nested ALFA+ cohort study. The ALFA registry constitutes of the basic demographic data of persons who desire to play an active part in the forthcoming BBRC projects. The parent cohort serves as the foundation for the emergence of research conventions and studies as it encompasses the cognitively normal participants aged between 45 and 74, who went through a series of cognitive tests and from that their clinical history, facts and details about their lifestyle and a blood sample were collected for further genetic analysis.

The methods used in this project consist of an Inclusion and exclusion criteria. The inclusion criterion was cognitively normal or standard Spanish and/or Catalan-speaking individuals aged between 45 and 74 years who agreed with all the study techniques and tests. Also, a close next of kin was engaged in the volunteer's functional assessment, with their consent. The exclusion criteria were: (1) Cognitive performance falling outside the established cut-offs, (2) Clinical Dementia Rating [CDR > 0], (3) Major psychiatric disorders or diseases affecting cognitive abilities (current major depression or general anxiety disorder, bipolar disorder, schizophrenia, and dementia), (4) Severe auditory and/or visual disorder, neurodevelopmental, (5) Significant diseases that could currently interfere with cognition (renal failure on haemodialysis, liver cirrhosis, active cancer in treatment), (6) Neurological disorders, such as Parkinson's disease [14] , stroke, epilepsy under treatment with frequent seizures(> 1/month) etc, (7) Brain injury that could affect the cognition: history of head trauma with parenchymal lesion, brain tumours, brain surgery,

or other causes that could cause acquired brain damage like cerebral chemotherapy or radiotherapy, and finally (8) suspected pattern of family history of autosomal dominant AD: three affected individuals in two different generations with onset before the age of 60 years.

Though the data obtained from biomarker and imaging studies support the existence of a preclinical phase of AD but in addition, disease-modifying pharmacological interventions on both mild moderate and late-stage AD persons are yet to exhibit significant clinical benefits. The ALFA project aimed at identifying the risk factors that may prompt the suffering or be suggestive of AD. Once the main non modifiable risk factors of AD (namely parental history and APOE genotype; Figure 3) and cardiovascular risk factors had been observed and assessed for the ALFA individuals, the researchers next determined their CAIDE dementia risk score, which is a well-established approach to identify the probability of dementia in late life.

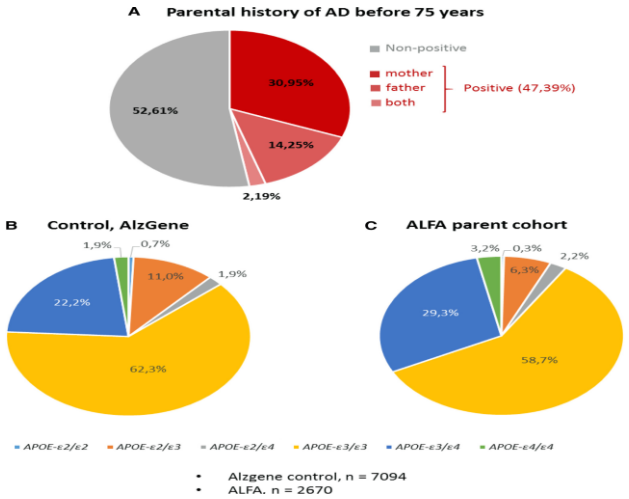

Figure 3: Non modifiable risk factors for Alzheimer's disease. (A) Pie Chart representation of the ALFA study participants' parental history of AD before the age of 75 years. Percentage of APOE genotypes in the ALFA parent cohort population (C) compared to the control (B)

The ALFA project have showed that parental history of AD is very essential as studies have revealed the confirmation of people with a genetic history of AD characterizes with a high risk factor for LOAD [Late Onset AD]. In view of the neuropsychological assessment of the ALFA parent cohort participants, the cognitive screening tests showed very useful data that was descriptive among age groups.

4. Contribution of glial cells to the development of Alzheimer's disease

One of the trademarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (neurons) that already exist in the brain. Amyloid is a general term for the synthesis of protein fragments in the body. Beta amyloid is a protein fragment that is snipped from an amyloid precursor protein (APP). Amyloid plaques usually

starts to surface during early phase of the Alzheimer's disease (AD), and they gradually develop and are highly dependent on the activated astrocytes and microglia. As a result, tangles are formed that destroy the vital cell transport system made of proteins.

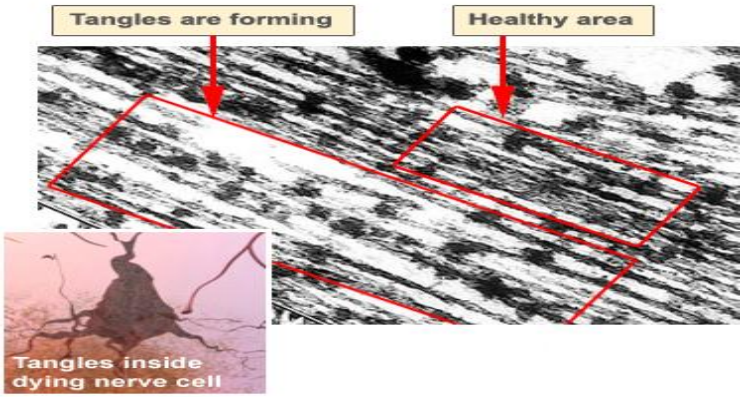

Figure 4: This electron microscope picture shows a cell with some healthy areas and other areas where tangles are forming.

In healthy areas, transport system is organized in orderly parallel strands somewhat like railroad tracks. Food molecules, cell parts and other fundamental materials travel along the "tracks." A protein named tau aids the tracks stay straight. In areas where tangles are forming: the Tau protein collapses into twisted strands called tangles, the tracks can no longer stay straight. They fall apart and disintegrate and nutrients and other essential supplies can no longer move through the cells, which eventually die.

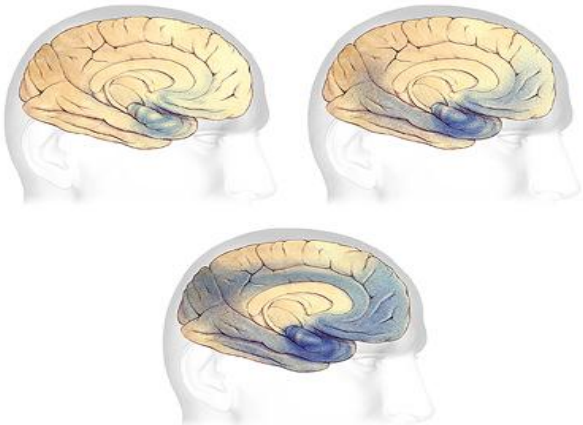

Figure 5: Plaques and tangles (shown in the blue-shaded areas) tend to spread through the cortex in a predictable pattern as Alzheimer's disease progresses.

Amyloid plaques are usually considered to be extracellular deposits of amyloid; however, new studies have suggested that neurons and glial cells can participate directly in their formation, growth and morphological evolution. One of the most controversial components of plaques is its associated microglia, which acts as a major element of brain inflammation in AD; The role that microglia plays in the advancement of AD mostly appeared to be a derivative of

blood monocytes and expressing monocyte/macrophage antigens. The collection of these cells in the lumen of local blood vessels and their migration through the walls of capillaries into the brain parenchyma is accompanied by distinct and rapid changes in their size and shape, and their co-localization with amyloid deposits in the walls of capillaries and perivascular amyloid plaques in AD brains.

Throughout AD brains, the actions of microglia and astrocytes are amalgamated and this fusion is detrimental and provides a major and direct contribution to the evolution of both the cell-derived and vascular amyloid plaques as well as to the local and global inflammatory responses. After thorough evaluation and focussed studies the researchers have delineated a proposed pathological sequence that highlights the specific contributions of these cells to both the formation and morphological evolution of plaques and the pathogenesis of AD in general (Figure 6).

The proposed pathological sequence stresses on the fact that intra neuronal Aβ42 accumulation is a key early event in AD pathogenesis.

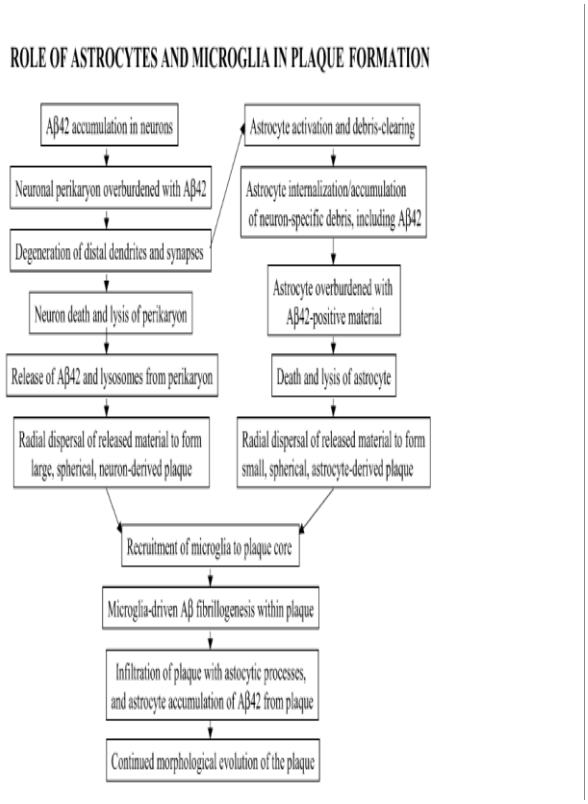

Figure 6: Flow diagram of the proposed sequence of pathological events.

5. Role of Inflammation in Alzheimer's disease

The disease Alzheimer's dementia[17,18] is considered as one of the most damaging genetic disease that especially became prevalent in the past few decades. A thorough microscopic examination on histologic sections of August D's brain by Alois Alzheimer showed not only the features of amyloid plaques and neurofibrillary tangles that have become the major characteristics of Alzheimer's disease (AD), but also glial cells that have clustered around the

plaques[19]. In the early 2000s, a study verified that individuals getting various nonsteroidal anti-inflammatory drugs (NSAIDS) for diverse systemic inflammatory ailments had a much less incidence and prevalence of AD but interest in the part played by neuro inflammation in AD has increased radically in the recent years.

Microglia, a type of glial cell located throughout the brain and spinal cord, account for 10–15% of all cells found within the brain. Microglias are key cells in overall brain maintenance they are constantly rummaging the CNS for plaques, impaired or unnecessary neurons and synapses, and infectious agents. Microglias actively responds to injuries and neurodegenerative disorders such as trauma or stroke and thus act as "warriors" or "nurturers". This phenotypic alterations result in both chemical and morphological changes. In AD brains, microglias are noticed to accumulate around neurotic plaques but appear to have a loss of phagocytic capacity and possibly obtain a toxic function as well. It is quite well known that AD is a very slow and gradual process with an interval between the onset of amyloid β (Aβ) deposition and dementia being approximately 20 years. Distinct heterogeneity in microglia/macrophage responses have been shown in the early stages of the dementia.

The role of astrocytes in AD pathogenesis is not so clear like the microglia. The astrocytes are considered to have a nutritional role and provide the structural support and a physical scaffold for neurons being the most common cell type in the central nervous system (CNS). However, now astrocytes are quite well known to have multiple active roles in normal neurophysiology, including significant involvement in neurotransmission, especially glutamatergic transmission. Similar to microglia, astrocytes also can be activated by various stimuli, and astrocyte activation is increasingly apprehended as an important element of neurodegenerative disorder.

Although a number of epidemiologic studies have linked anti-inflammatory treatment to lower AD risk, prospective clinical trials with NSAIDs and some other types of anti-inflammatory agents so far didn't get success to demonstrate any effectiveness. The scientists have claimed that in the near future a prospective field for further research is to define the characteristics and significance of neuro inflammation at different stages of AD as it is becoming quite clear that the innate immunity is pathogenically important in AD and possibly even key for the disease progression.

6. Conclusion

Since Alzheimer's is a progressive disease, so eventually with time, all the components of brain are susceptible to damage. As this happens, more symptoms develop. They also become more severe. But diagnosing Alzheimer's at an early stage is a challenging task and still several researches are being going on in this field. Some of the methods discussed in this paper have helped to successfully identify the disease and thus starting treatment at an earlier stage.

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