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A Study on Alzheimer's Using Machine Learning

Siva Krishna Kalluri[1], Hari Krishna Deevi[1], Akhila Kalluri[2]

[1]*Research Scholar, Department of Computer Science and Engineering, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.*

[2]*Assistant professor, G V R & S College of Engineering & Technology, Budampadu, Andhra Pradesh.*

Correspondence E-mail Id: *editor@eurekajournals.com*

Abstract

Alzheimer's disease is the most common form of dementia, defined as a general category for diseases affecting the brain's activities and pathways. Alzheimer's disease came about 100 years ago when Alois Alzheimer gave a lecture in Germany on the first case of what is now referred to as Alzheimer's disease. He described the typical characteristics of the disease to include certain memory disturbances and instrumental signs. He, furthermore, showed a neuropatho-logical picture with military bodies, known as plaques, and dense bundles of fibrils, known as tangles. This discovery became one of the major breakthroughs of the disease that allowed for further research and findings (Blennow et al. 2006).

Introduction

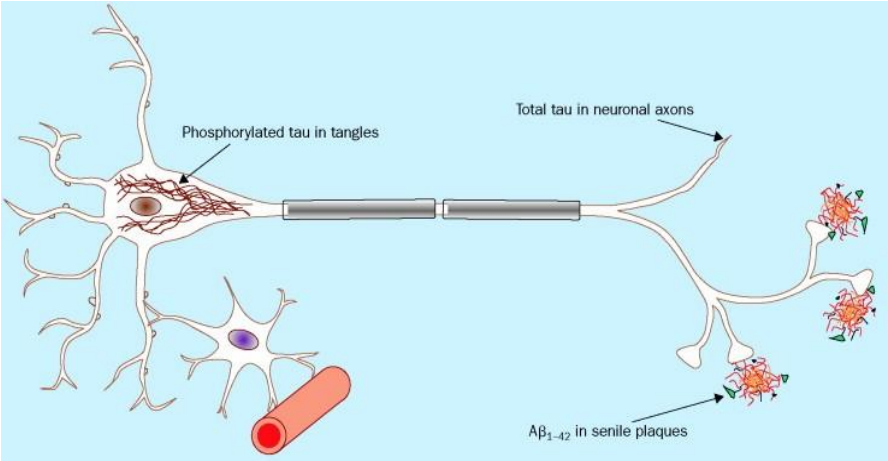
Alzheimer's disease is one of the most prevalent diseases, accounting for about 50-60% of all dementia cases, making it a major health problem, especially among people 85 years or older for whom there is known to be an exponential increase in contracting the disease. [1] With the increased life expectancy, the number of people suffering from Alzheimer's disease is expected to double every 20 years, predicting up to 81 million cases in 2040 as a result of this. Among the most well known factors for this disease is ageing along with other possible risk factors including reduced brain size, low educational and occupational attainment, low mental ability in early life and reduced mental and physical activity during late life (Blennow et al. 2006).

Moreover, although some cases of Alzheimer's disease have been attributed to genetics, the vast majority of them are not genetically inherited although some genes can act as risk factors. Some of the genetically identified forms, which include familial/early onset and sporadic/late onset cases, have been seen in patients under the age of 65, accounting for a total of 0.1% cases. [2] In addition to genetic factors, studies have indicated the role of environmental effects, diabetes, hypertension, smoking, obesity, history of brain trauma and cerebrovascular disease on the increased risk for Alzheimer's disease (Duthey 2013).

Some of the core clinical features of Alzheimer's disease include gradual and progressive decline in memory, executive function and the inability to perform daily activities. Some of the clinicopathological studies [3] suggest the presence of a long preclinical phase of Alzheimer's disease with its pathology beginning a decade or so earlier before the onset of cognitive symptoms and even before patients are brought to any medical attention. Significant impairment in short-term memory with the inability to retain new information is the most common presentation for individuals with Alzheimer's disease. Some of the characteristic reports of short- term memory loss include the repetition of questions or statements, frequently misplacing items and difficulty remembering new people. Moreover, individuals with early onset of the disease experience difficulties with certain executive functions such as planning and organizational skills, judgment, problem solving and handling complicated tasks. They are also shown to have language impairment with reduced verbal fluency, word-finding difficulty and hesitancy of speech. As a whole, individuals in the early stages of Alzheimer's disease appear normal to casual inspection and are able to perform most tasks independently. In contrast, individuals with moderate and severe Alzheimer's have progressive decline in cognitive functions with more severe functional impairment and depend on others more for daily activities. They have pronounced difficulties in retaining new information and are often described as "living in the past." Disorientation also becomes more pronounced in which individuals may be unable to recognize family members or relatives. Their logical reasoning is severely impaired and begin to present certain behavioral symptoms such as hallucinations, illusionary misidentification, temper tantrums, verbal and physical aggression, anxiety or restless activities. During the severe stages of the disease, all cognitive functions are lost, and individuals become dependent on nursing care as a result of their need for assistance for simple activities such as eating and care for hygiene.Most patients at this stage are bedridden and die of complications of aspiration or infection (Tarawneh and Holtzman 2012).

The pathogenesis of the disease was first identified at the microscopic level of the characteristic lesions in Alzheimer's disease that are senile or neuritic plaques and neurofibrillary tangles. Degeneration of the neurons and synapses in the medial temporal lobe structures and cortical areas of the brain led to some understandings of the pathologic processes. Many hypotheses have been suggested explaining this degeneration including A□ aggregation and deposition with plaque development, tau hyperphosphorylation with tangle formation, neurovascular dysfunction and other mechanisms such as cell-cycle abnormalities, inflammatory processes, oxidative stress and mitochondrial dysfunction (Blennow et al. 2006). The identification of the role of the Amyloid -peptide (A), known as the sticky peptide in the brain plaques, [4] through the sequencing of meningeal blood vessels of Alzheimer's disease patients, marked the beginning of the modern era of neurodegenerative disease research. Moreover, the cloning of the gene encoding the □-amyloid precursor protein (APP) and its earlier recognition that Downs syndrome leads to the neuropathology of Alzheimer's disease led way to the proposal that A accumulation is the primary event in Alzheimer's

disease pathogenesis. This amyloid hypothesis is further supported by the deposition of the microtubule-associated protein tau and its role in the formation of neurofibrillary tangles that are associated with Alzheimer's disease (figure 1). [5] As the most severe alterations in the tau protein are not sufficient to aid in the formation of amyloid plaques in Alzheimer's disease, it is suggested that these neurofibrillary tangles must have been deposited after initial plaque formation. Studies on the relationship between an abnormal hyperphosphorylation of the tau protein and its effect on the neurofibrillary tangles, specifically among patients with Alzheimer's disease, have been examined (Hardy and Selkoe 2002).



Source: Blennow Kaj, Hampel Herald. 2003. CSF markers for incipient Alzheimer's disease. The Lancet Neurology 2(10): 605-613

Figure 1.Drawing of a neuron depicting the central processes responsible for Alzheimer's disease including the phosphorylated tau in tangles and Amyloid □-peptide in plaques

The tau protein is located in the neuronal axons with many phosphorylation sites (Blennow and Hampel 2003). [6] In healthy neurons, the tau protein stabilizes the microtubules, which make up the cytoskeleton of the cell, through phosphorylation and dephosphorylation of the protein. The hyperphosphorylated tau proteins, which are known to be abundant in patients with Alzheimer's disease, are unable to bind to microtubules and rather polymerize other tau molecules, resulting in the formation of straight filaments, which subsequently may cause failure in neuronal transport and lead to certain pathways that may result in cell death. Such disruptions in the metabolic pathways include increased oxidative stress and altered calcium levels, which result in certain apoptosis dependent and independent cell death processes (Revett et al. 2012).

The first study that reported tau protein concentration in cerebrospinal fluid as a biomarker for Alzheimer's disease was published in 1993. Since then, methods based on monoclonal antibodies have been used to detect all forms of the tau protein, including the phosphorylated type. Such diagnostic markers, for detecting Alzheimer's disease are classified under two groups as state markers and stage markers, both of which allow for the detection and progression of Alzheimer's. State markers, in particular, [7] reflect the intensity of the

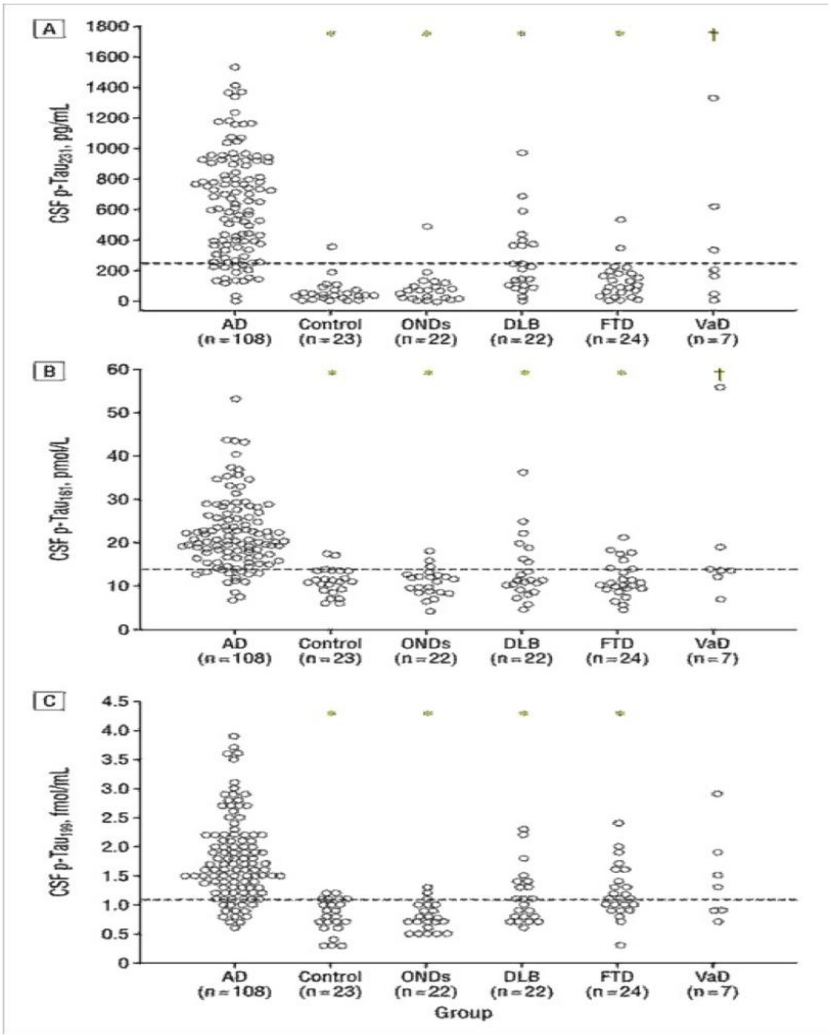
neuronal damage and degeneration, and the total concentration of tau protein in the cerebrospinal fluid is an example of this. Cerebrospinal fluid is obvious source of biomarkers for Alzheimer's disease as it is in direct contact with the extracellular space of the brain in which biochemical changes, such as A□ in plaques or the hyperphosphorylation of tau, in the brain are shown through the cerebrospinal fluid. As a whole, the concentration of the phosphorylated tau protein in the cerebrospinal fluid is a marker for neuronal damage as well as reflecting the phosphorylation state of tau and the formation of tangles in Alzheimer's disease (Blennow and Hampel 2003).

One study, in particular, focuses on the use of monoclonal antibodies for the different phosphorylated epitopes of tau through enzyme-linked immunosorbent assays to measure the cerebrospinal fluid concentrations of the phosphorylated tau protein (p-tau) in cerebrospinal fluid. The three different immunoassays used are specific for the phosphorylated epitopes threonine 231(p-tau231), threonine181 (p-tau181) and and serine 199 (p-tau199). [8] Evidence from previously conducted pilot studies on these phosphorylated epitopes suggests that the quantification of the phosphorylated tau protein could help to improve early detection, diagnosis and tracking the progression of Alzheimer's disease. [9] These phosphorylated epitopes, particularly p-tau231, distinguished between patients with Alzheimer's disease and those with other neurological disorders with a sensitivity of 85% and a specificity of 97%, suggesting its role as an effective biomarker candidate for Alzheimer's disease. [10] This more recent study thus tested the diagnostic accuracy of the 3 p-tau assays through cerebrospinal fluid concentrations. It was the first comparative study to apply of the three immunoassays in detecting the different p-tau epitopes using the same set of controls and patients to compare both individual and combined diagnostic accuracy (Hampel et al. 2004).

A total of 206 individuals were studied with 108 patients with probable Alzheimer's disease and 53 with other dementia disorders in which the structural and functional imaging results were consistent with the diagnoses in these patients. Twenty-three patients were taken as controls in the study whose medical history, blood tests and results from physical examination and other medical tests were examined. Samples of 1ml cerebrospinal fluid from patients were obtained through a lumbar puncture. [11] The levels of p-tau231 were measured using an enzyme- linked immunosorbent assay, which uses a combination of CP27, Tau-1 and CP9 that recognize respective amino acid sequences. The levels of p-tau181 and p-tau199 were measured using a sandwich enzyme-linked immunosorbent assay method (Hampel et al. 2004). [12]

Results and Discussion

The results indicate that all p-tau subtypes were significantly increased in patients with Alzheimer's disease when compared to the other groups studied (figure 2).



Source: Hampel H, Buerger K, Zinkowski R, Teipel S, Goernitz A, Andreasen N, Sjoegren M, DeBernardis J, Kerkman D, Ishiguro K, et al. 2004. Measurement of Phosphorylated Tau Epitopes in the Differential Diagnosis of Alzheimer's Disease: A Comparative Cerebrospinal Study. JAMA Psychiatry 61(1): 95-102

Figure 2. Levels of cerebrospinal fluid in the phosphorylated tau protein epitopes p-tau231 (A), p-tau181 (B), and p-tau199 (C). The dashed lines represent the cutoff level when the sensitivity was set at 85% or higher. Patients with Alzheimer's disease had higher levels of all p-tau subtypes when compared to the control patients, patients with other neurologic disorders (ONDs), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and vascular dementia (VaD).

Moreover, all the p-tau proteins met the sensitivity levels of 85% in detecting the progression of Alzheimer's disease in terms of the formation of tangles when compared to the controls and those patients with other neurologic disorders. When comparing the diagnostic accuracy among the p-tau proteins, all of them showed high discriminative power for Alzheimer's disease than the group with all other non-Alzheimer's diseases, especially for p-tau231. When examining group diagnostic accuracy with a combination of p-tau markers, a combination of p-tau231 and p-tau181 showed to have a slight increase in specificity when

compared to their respective specificities alone; however, as a whole, the combination of the three markers did not add a great extra discriminative power. However, the study did report that the concentrations of all 3 p-tau proteins were significantly greater in patients with Alzheimer's disease than those with other groups studied. Referring back to the diagnostic accuracy of these proteins, it can be concluded that using this method of p-tau proteins to discriminate between Alzheimer's disease and other forms of dementia is effective as a whole (Hampel et al. 2004).

With the increase in research and methods in early detection of Alzheimer's disease, the use of p-tau phosphorylation provides a viable way to distinguish early stages of Alzheimer's disease for clinical diagnosis (Hampel et al. 2004). It can also possibly allow for distinguishing patients with mild cognitive impairment who are likely to progress into Alzheimer's disease as a result of its high sensitivity, specificity and predictive values, thus explaining its potential for pre-clinical Alzheimer's disease. However, these main feasible biological markers are in an ever- maturing development process, suggesting the role for potential future research in providing objective and reliable ways of drug safety and treatment efficiency in drug trials. Since the neuropathological changes for Alzheimer's disease appear well before any symptoms, biomarkers of pre-clincal Alzheimer's disease are likely to be actively researched into in providing therapies in future generations (Hampel et al. 2010). Early recognition and treatment is crucial in the potentiality for reducing and possibly even reversing some of the effects that Alzheimer's disease causes among patients, both pathologically and cognitively. This interest for future research significantly increased with the introduction of certain symptomatic treatments, such as the use of acetylcholine esterase (AChE) inhibitors and other drug therapies, that attempt to mitigate the effects of Alzheimer's disease, paving ways for further research opportunities in understanding the role of biomarkers (Blennow et al. 2006).

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