Alzheimer’s Disease and Medical Imaging: A Case Report

Abstract

This case report focuses on the various ways to diagnose Alzheimer’s disease through the use of medical imaging. The extraction of cerebral spinal fluid as demonstrated in lumbar puncture fluoroscopy can measure the quantity of amyloid beta peptides. Fluorodeoxyglucose-positron emission tomography scans are also used to specify brain metabolism of individuals living in different stages of Alzheimer’s disease. Magnetic resonance imaging acquires volumetric studies to measure the hippocampal size and atrophy rate. Clinical trials have been established using the double-blind placebo effect for possible treatments. Some research also shows a predetermined risk for Alzheimer’s disease through genetic tracing, abnormal glycaemia levels, poor diet and exercise, and exposure to prolong anesthesia.

Literature Review

Currently, 35 million people worldwide are affected by dementia, in the absence of new treatment breakthroughs, 80 million cases are predicted by 2040. Alzheimer’s disease (AD) is a neurodegenerative disease that most commonly results in confusion, forgetfulness, mood swings, and hallucinations. There is no cure for AD, but with the help of modern medicine and technology physicians are able to diagnose and use preventative measures before it is fully established. Through the use of various tests, patients can be identified as either mild cognitive impairment (MCI), AD, or advanced AD. If AD is diagnosed in premature stages, therapeutic medicines and clinical trials can be used to delay the neurodegenerative disease and enhance brain metabolism and function.

In this literature review, cognitive decline will be defined and compared to other similar diseases apart from AD. It will also elaborate other categories at risk for developing AD such as abnormal glycaemia levels, genetic variability, and anesthesia affects. Strengths of particular medical imaging such as the use of magnetic resonance (MR), fluorodeoxyglucose-positron emission tomography (FDG-PET), and cerebral spinal fluid (CSF) extractions will be demonstrated in greater detail as some of the few methods that can determine neurodegenerative stages. Since AD is ultimately a life-threatening disease, certain end-of-life care has been available with individuals at advanced stages. People living with AD are more susceptible to
illnesses such as pneumonia, dysphagia, delusions, emotional distress, and loss of speech.\textsuperscript{2} Pharmaceutical medicines and therapeutic involvement have been used to enhance the final days for these individuals. Clinical trials and drugs have also been created and observed to reduce plaques and tau tangles. Through trial and error, research is coming closer and closer to a reversible AD.

\textit{Cognitive decline and general anesthesia}

MCI is shown in individuals who have frequent loss of memory, confusion, and language. These symptoms are a result of inadequate metabolism of glucose to the brain and, if not diagnosed promptly, can be irreparable and cause neurodegeneration. The symptoms of MCI are not always directed to AD. Cognitive decline can also be a factor for Huntington’s disease, Parkinson’s disease, or Pick’s disease.\textsuperscript{1} Further testing through medical imaging, patient history, genetic tracing, and CSF can provide a definite answer to the various cognitive impairments.

There are some instances where cognitive decline can be generated through the use of anesthetics. Postoperative cognitive dysfunction (POCD) is a risk for elderly patients undergoing general anesthesia. Studies suggest that general anesthesia can increase Aβ peptides, senile plaques, and tau tangles. Patients undergoing invasive procedures with prolong anesthesia, such as heart surgery, have a greater risk for developing POCD. This condition is critical in patients who may be experiencing premature AD and can lead to poor functional recovery, prolonged length in the hospital, decreased patient quality life, and increased mortality after surgery.\textsuperscript{3} Symptoms include confusion and delirium and may or may not worsen over time. Memory decline can be evident for weeks, years, or a lifetime from the effects of anesthesia. Risk versus benefits must be well contemplated and the patient must be fully aware of post-operative complications.

\textit{Diabetes}

Cases of individuals diagnosed with diabetes have reached the highest ever recorded, and continues to escalate over time. It has been proven that diabetes and Alzheimer’s disease are directly related. The brain needs an adequate amount of glucose for successful metabolism and production of neurons. Inadequate glucose can cause dysfunction and impairment to the brain. Hypoglycaemia is a decline in glucose to the brain and alters brain function. This can cause
confusion, unusual behavior, poor concentration, drowsiness, poor coordination, visual disturbance, and tingling around the mouth. Hyperglycaemia can cause significant lasting damage to the neurons in the form of visible lesions in the brain. Type 2 diabetes is more dominant in people with Alzheimer's disease due to the increased protein deposition in the brain and pancreas. Tighter glycemic control can improve cognitive impairment in individuals living with type 2 diabetes. High blood pressure, heart disease, stroke, high cholesterol, and diabetes can cause damage to the cerebral, coronary, and peripheral blood vessels. These symptoms, if uncontrolled by prescription, can cause stroke – which can cause neuronal damage to the brain.

**Genetic tracing**

The e4 allele of the apolipoprotein E gene (APOE) is found in chromosome 19 and is known to be the chief genetic risk factor for Alzheimer's disease. APOE e4 allele is among the carriers of the APOE e3 allele. A test using MR was conducted to compare the two alleles to determine the relation between brain responses. Subjects were asked to memorize and recall unrelated pairs of words while subjects rested between such periods. As shown in Figure 1, the APOE e4 allele had greater magnitude and brain activation in regions affected by AD. These regions included the left hippocampal, parietal, and prefrontal regions. Studies have shown that the cause for greater signal intensity in the hippocampal region is an increased effort to achieve the same level of performance as subjects who do not have a genetic risk.

**Prevention**

Most AD cases are a result of vascular dementia, which is permanent damage to the heart or blood vessels. Conditions that cause damage to the heart or blood vessels include high blood pressure, heart disease, stroke, diabetes, and high cholesterol. Autopsy studies demonstrate that about 80% of individuals with AD also have cardiovascular disease. Plaques and tangles may be present in the brain without causing symptoms of cognitive decline unless the brain also shows evidence of vascular disease. According to the Alzheimer's Association Web site, about 20% to 25% of the blood from every heartbeat is carried to the brain. Neurons use at least 20% of food and oxygen received. Since the brain supplies the richest network of blood vessels, it is important to intake adequate nutrition. “Brain Food” is considered to be a Mediterranean diet high in whole grains, fruits and
vegetables, fish, nuts, olive oil, and other healthy fats. Exercise increases blood and oxygen flow, which may protect brain health through its proven benefits to the cardiovascular system. Studies also indicate that maintaining strong social connections and keeping mentally active may also decrease risk for cognitive decline.

**How FDG-PET can determine premature AD**

Single photon emission computed tomography (SPECT) has historically been the modality of choice for examining this disease; however, PET is becoming more prevalent and useful in the evaluation of AD. PET is preferred for AD observation because it accentuates metabolism, includes a better spatial resolution, and has the ability to quantify changes. Postmortems of the brain demonstrate a thin cerebral cortex, senile plaques, and neurofibrillary tangles.

According to Mehta and Thomas, PET can reduce the false positive rate from 23% to 11% with the combination of clinical criteria. It can be used to differentiate AD from treatable forms of dementia such as toxic metabolic states, depression, and normal pressure hydrocephalus. Before AD is fully established, a patient can present premeasured symptoms known as MCI. In this stage, the patient frequently expresses confusion, mood disorders, and forgetfulness. MCI and AD can best be detected through the use of FDG. As a glucose analogue, FDG reflects cerebral glucose metabolism (see Figure 2). It is the most commonly used agent in PET imaging because it best demonstrates hypometabolism rate and activity. To prevent false positives, the patient is kept in a stress-free, semi-dark atmosphere to minimize activation of the visual cortex and other brain centers. Recent studies of larger patient populations suffering from AD demonstrate 93% to 95% sensitivity to FDG. The glucose metabolism of FDG will decline more presumably in patients with AD rather than MCI. “Patients with abnormal results on FDG-PET and with abnormal episodic memory were 11.7 times more likely to progress from MCI to AD.”

A negative PET scan signifies an unlikely advancement of AD for a mean of 3 years with those that initially expressed MCI.

PET used in the early stages of AD can contribute significantly to diagnoses and future treatments. Data suggest that including PET in the diagnostic process can result in more cost-effective and accurate diagnoses, particularly in differentiating AD from other forms of dementia. The use of the FDG glucose agent can provide sufficient information by observing the
metabolic rate and activity. This advanced method of diagnosing AD earlier, before the disease progresses, can provide hope and a better prognosis for the patient.

**How MR can determine premature AD**

As defined by the authors Frankó and Joly,“Alzheimer’s disease is associated with the widespread deposition of amyloid plaques and neurofibrillary tangles in the brain.”(p.7) These neuropathological changes cause neuronal loss in the entorhinal cortex and hippocampus, decreasing the size and volume of the hippocampus. MR is a more direct way of measuring the atrophy of the brain by repeated scans within the same individual. This can be used to monitor the progression for individual patients. Volumetric studies use a longitudinal dataset to report a higher rate of hippocampal volume loss in patients with AD when compared to elderly healthy patients and patients suffering from MCI.

In this study, healthy patients, patients with AD, and patients with MCI had duration of 200 days between the first and last exam. The use of a single scan MRI prevents the investigation of atrophy evolution; therefore, a 3 dimensional (3D) image of the hippocampal surface was abstracted using various points on the hippocampus and the amygdala based on the histological examination and post-mortem studies of the same brain. Based off the results performed by the authors, the AD group had the most significant hippocampal volume lost and atrophy in the lateral side of the hippocampal head. In addition, the AD patients also proved to have a smaller hippocampus as compared to the healthy elderlies and MCI group. Progressive MCI patients had a higher atrophy rate when compared to stable MCI patients (See Figure 3 for visual comparison of atrophy rates). The regions that have the highest burden of neurofibrillary tangle and neurophil tread depositions also reflect the highest atrophy rate in the study. Based on the atrophy rate on the lateral side of the hippocampal head, studies have shown that it is found to be the best predictor of the progression of MCI to AD. This can determine the risk of patients with an early phase of AD and can seek treatments that are mainly effective in the early phase.

As noted, the regions showing the highest atrophy rate correspond to those that were described to have the highest burden of tau deposition and developing AD. Premature AD can be detected and diagnosed by using longitudinal MR and conducting measurements of the hippocampal atrophy rate. As a result of how individuals vary in accordance to the size and shape of the hippocampus, frequent MRs of that individual should be performed to evaluate the
progression of AD. Test disease-modifying drugs can be developed to stop the progression of AD based on longitudinal MR screenings.

**Amyloid (Aβ) peptides in CSF**

AD is also caused by an imbalance in the production of amyloid beta (Aβ) peptides. There is no cure for this disease, but with the help of modern medicine and technology there are relevant indications that pre-AD, or MCI can be diagnosed before advanced AD is fully established. The use of bodily fluids, such as CSF, contains protein-rich information that reflects neuronal features. These protein-rich biomarkers are known as Aβ peptides and are significant in neuronal plasticity and information handling. Once extracted and measured, Aβ peptides can conclude the neuronal structure for MCI and advanced AD patients.

CSF contains certain biomarkers essential to the diagnosis of AD. “Biomarkers are parameters (physiological, biochemical, and anatomic) that can be measured in vivo and reflect specific features of disease-related pathophysiological processes.” Aβ peptides are the biomarkers found in CSF that play a crucial role in physiological memory of the hippocampus. Extracellular amyloid plaques, axonal degeneration, and intraneuronal tangles are the three major alterations in an AD brain that can be monitored with CSF biomarkers. The deposition of the peptide in plaque is considered the primary cause for the decrease in CSF levels seen in AD. Aβ peptides are not only involved in information handling, but they also trigger out central nervous system (CNS) plasticity. Plasticity in the CNS is a pattern in structure and function as a result of development, experience, or injury. Neurodegenerative diseases cause the need for plasticity for CNS repair; however, it is also referred to as a “double-edged sword” in that it reduces neuroprotection, causing a reduction in neuronal plasticity. Aβ peptides are secreted at a higher rate to maximize neuronal plasticity seen in AD and other neurodegenerative diseases.

AD causes a need for more Aβ peptide secretions and neuronal plasticity, but the degeneration of the brain is so prevalent that it becomes irreparable. Through the use of CSF and Aβ peptide extractions, scientists are able to obtain an insight look at the cellular function in AD neuronal activity and degeneration. Aβ peptides play a crucial physiological role in neuronal survival and may be the most reliable biomarker to monitor the biochemical effect of disease-modifying drugs in AD clinical trials. AD can be detected and diagnosed earlier with this
method, which could ultimately change the prognosis for individuals living with this neurodegenerative disease.

**Clinical Trails**

More and more data has been established to further advance clinical trials. In order to obtain such viable data, participants must fall under a certain category in order to be selected for a clinical trial. They must be limited to certain age range, must be in a certain stage of the disease, are not allowed health conditions other than the one being studied, and must not permit use of other medications. Any change in the above conditions can alter the effect and overall consensus of the drug. The FDA requires that possible participants sign an informed consent which includes complete understanding of the risk and benefits of the drug and answers to any question. Participants are free to leave the study at any given time. Trials are considered “placebo-controlled” meaning that participants are randomly selected to receive the experimental treatment and some receive the “placebo” or inactive pill. Trials are “double-blinded” in that both the physician and the participant are unaware who receives the drug or the placebo.

There are four trials categories that particular volunteer subject fall under. Phase one clinical trial is the first stage of human testing. This typically involves fewer than 100 healthy volunteers; studies involve the risk and side effects of the new clinical drug. Phase two trial has a few hundred volunteer who have the condition the drug is designed to treat. Results pertain to safety and the best dosage of the drug. Phase three trial has several hundred to thousands of volunteers enrolled. These are commonly a worldwide clinical trial. The results provide the chief evidence for safety and effectiveness that the will be considered for FDA approval. Lastly, phase four of trials is known as the *post-marking* studies and is required once an FDA drug is approved. Researchers continue to monitor the health of people taking the medication to gain further insight into its long-term safety and effectiveness.  

**Prognosis**

Many findings have contributed to reparable AD; however, there is no definite cure to this neurodegenerative disease. Research has supported possible treatments and preventative measures used to decline the rate. Since evidence of plaques and tau tangles can be diagnosed a decade before obvious symptoms occur, it should be treated right away before it continues to
degenerate dendrites and neuronal activity (see Figure 4). Apart from plaque, tau tangles must be the other target for drug development to prevent advanced formation. Metals in the brain such as copper and zinc help drive the production of plaques and tangles. A recent drug trial known as PBT2 prevents these metals from occurring. “According to an interview with Dr. Tanzi in the Harvard’s Health Letter12 “…PBT2 takes the metal away from the amyloid protein so it can’t form plaques. It removes metal that was trapped and makes it available again for dozens of brain functions like gene activity and antioxidant health. PBT2 also keeps tangles from forming. And finally, it induces new neurons to grow in the hippocampus, which should improve executive function,”(p.1) An initial animal trial and 2 clinical trials encouraged his findings through evidence of significant improvement in executive function of overall memory in 12 weeks. In a combination with medical imaging and the pharmaceutical drug PBT2, evidence supports that this new drug is successful in removing amyloid plaques and optimizing brain recovering and memory growth. If the drug proves effective in larger studies, Tanzi10 is hopeful it will be available to people with AD in about five years.

As for now, the only cure available to individuals living with AD is a peaceful environment and preparation. End-of-life diseases can be hard on both the patient and family. Medical professionals have specialized in providing efficient care to the patient and their families. Palliative care is also known as comfort or hospice care and is recommended for end-of-life quality care with available therapies for intended pro-long life. According to the World Health Organization,13 palliative care is “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.”(p.85) Preparing families for death is a way to improve care and provide the families with a sense of closure to prevent family depression and complicated grief. There are some measures that can be restricted so the patient can have an easier passing. According to Mitchell et al,14 some symptoms present include high and increasing levels of pain, dyspnea, agitation, aspiration, and pressure ulcers. Therapeutic medicines and treatments can reduce the distress caused by the previous symptoms.
Conclusion

AD is a life-threatening illness and affects millions of people worldwide. There is no cure for advanced stages, but if detected prematurely physicians can attempt to decline the rate of atrophy and neurodegeneration. Some factors such as CSF levels, genetic testing, and patient history play a significant role in detecting AD before it progresses. The use of medical imaging as seen in MR and PET have also greatly expanded the resources and diagnosing capabilities. Good health through diet and exercise, high brain activity, and socializing can reduce the chances of developing AD. With these new methods, mortality rate can be reduced and lives can be better enhanced.
References


Figures and Captions.

Figure 3. Hippocampal atrophy rate of patients presented with AD (A), MCI (B) and controls (C). Individual monitory using MRI is measured in mm/year according to the left and right hippocampi atrophy. Degeneration is represented by blue and increases in volume in patients under category AD (A). Image courtesy of: Frankó E, Joly O. Evaluating Alzheimer’s Disease Progression Using Rate of Regional Hippocampal Atrophy. *PLoS ONE*. 2013;8(8):1-11. doi:10.1371/journal.pone.0071354.g002