Role of PET Scan in Diagnosis of Alzheimer's Disease: Evidence-Based Medicine

Dyuti Venkat

Introduction

According to the CDC, Alzheimer's Disease is a neurological condition caused by the build-up of abnormally folded proteins, affecting 5.8 million individuals in the USA alone, with age being the most prominent risk factor. In Alzheimer's, proteins fail to function normally and disrupt surrounding neurons in the brain, leading to brain atrophy. AD is the most common cause of dementia, memory loss, cognitive decline, and behavioral changes that interfere with day-to-day life, accounting for 60-80% of all dementia cases. Symptoms include impairments in memory, thinking and reasoning, executive decision-making, and personality changes, but since the disease is progressive, skills like listening to music and telling stories tend to be preserved until later. In addition to memory loss, patients usually develop brain inflammation and oxidative stress. (cellular damage by free radicals—toxic oxygen molecules) The prognosis of AD is approximately 3-11 years after diagnosis, with some patients reported living over 20 years after diagnosis, underlying the heterogeneity in the disease progression. [1]

Risk factors include age, family history and genetics, Down Syndrome, and Head Trauma, among others. The risk increases with age, (most patients are 65+) the presence of the Apolipoprotein E gene form (APOE 4), or a first-degree relative patient. Although aging is the most renowned risk factor for Alzheimer's, it is not a natural attribute of the aging process. In addition, although uncommon, younger individuals are affected as well, and although much of the complexity of these genetic mechanisms remains unexplained, markers like the apolipoprotein E gene (APOE), specifically APOE e4, which is carried by 25-30% of the population, can help identify patients at risk for developing AD. Down syndrome (Trisomy-21) patients are at a high risk of developing all sorts of health complications throughout life, including Alzheimer's, with the presence of 3 copies of the genes that produce beta-amyloid underlying a possible connection between the two. Mild Cognitive Impairment (MCI) is a form of cognitive skill set loss, which includes abnormally high memory loss; while not handicapping in social environments, it can cause problems later on, including dementia; traumatic brain injuries (TBI) have also been found to increase AD risk. Finally, animal studies show that air pollution might also affect one's risk of AD, especially traffic pollution and firewood. [2]

Amyloid (beta-amyloid 42) and Tau are the most well-known neuropathological hallmarks, with amyloid causing plaques and tau forming neurofibrillary tangles. According to PubMed, Tau is phosphorylated, folding the monomer (tau) into the polymer (tangles), resulting in carboxyl and amino groups shortening, and unaligned folding. [3]

Making the diagnosis is complicated, as only a brain autopsy can give a definitive diagnosis. As a result, Alzheimer's often goes undiagnosed for years, when patients could receive life-sustaining treatments, highlighting the need to develop novel biomarkers for diagnosis and prognosis, leading to medical practitioners' reliance on other diagnosis methods, including cognitive testing and brain imaging. [4] Currently, biomarkers are limited, due to high cost and restricted access. ***This review article will focus on different types of imaging used in the diagnosis, identification, and treatment of Alzheimer's Disease.***

Identification of Alzheimer's

Memory impairment, particularly the memory of events occurring at a particular time/place and recent events, is the most common initial symptom of AD dementia because AD first impacts the hippocampus and other medial temporal lobe structures. [5] By comparison, immediate memory (considered independent of hippocampal function) is not affected until later in the disease course. [6] In the early stages, executive function impairment ranges from prominent to subtle. [7, 8] Typically, the inability to complete tasks or multitask emerges. Reduced insight into deficits (anosognosia) is common, as patients often over- or underestimate their deficits due to lack of insight, and often come up with explanations for them. As a result, an informant's opinion, typically a family member or care worker, is often necessary. [9, 10] Visuospatial impairments, language deficits, neuropsychiatric symptoms (apathy, social disengagement, and irritability) behavioral disturbances (agitation, aggression, wandering, and psychosis) difficulty performing learned motor tasks, changes in smell, sleep disturbances, seizures, and some motor signs, progressive language difficulty are other later symptoms. [11-16]

Several diagnostic tests are available for the identification of AD. Commonly, patients have to recall a series of words or objects immediately and then after 5 minutes, and "by about recent events and orientation." The Montreal Cognitive Assessment (MoCA) helps with diagnosis and management and assesses "several domains" of cognitive thinking, compared with the MMSE (Mini-Mental State Examination). The typical cutoff score is 26 but should be adjusted based on education and other factors. [17] Diagnosis cannot be made based on low scores alone; the most essential part is a detailed history, the perspective of an informant, (to document the preservation or loss of independent function), and neuropsychiatric symptoms. [18] The next section will focus on objective testing, to help rule in or out other forms of dementia.

Diagnosis of Alzheimer's

While AD has been historically difficult to identify and diagnose early in its course, diagnostic accuracy has increased recently, with a specialized PET scan, to 100% specificity & 96% sensitivity in AD, even in milder patients. [19] Biomarkers indicate normal biological (pathogenic processes included) and pharmacological effects from therapy. [20, 21] In AD, they are used to determine diseased conditions and overall health, using PET of tracer molecules and analysis of CSF protein. [22] Hyperphosphorylated tau 181, P-tau181, is secreted in the brain, and CSF and extracellular deposition of amyloid-β (Aβ) can be used as a prognostic biomarker. [23, 24] CSF examination for p-tau, Aβ42, and total tau protein content is inexpensive, with 85-90% accuracy, but takes longer, due to invasive methods and the plethora of facilities involved in fluid analysis. Florbetapir, florbetaben, and flutemetamol are alternative testing options but due to high cost, are not widely used. However, both tests exhibit similar accuracy, so the optimum test depends upon patient/provider preference, (cost and facility availability). A recent study found that pathological changes can be seen on MRI beginning two decades before symptoms and so, diagnosis on the onset of symptoms is not ideal, as irreversible damage would already occur. The development of novel biomarkers is required to identify the disease before irreversible damage occurs. [25]

INNOTEST, an ELISA assay has been used to quantify t-tau, p-tau, and Aβ42 in CSF revealing a unique 'Alzheimer's CSF profile' with an increased level of t-tau and p-tau and decreased Aβ42 level allowing for comparison with other patients and hopefully leading to early detection of AD patients. [26, 27] Plasma Aβ42 and Aβ40 levels have become validated biomarkers for AD detection and diagnosis. [28] Another strong biomarker is amide I, with a positive likelihood ratio of 7.9 for AD diagnosis. Amide I have been shown to increase before the onset of dementia symptoms, making it an extremely attractive option for AD diagnosis. [29] Other potential biomarkers include complement component 1q (C1q), macrophage migration inhibitory factor (MIF), soluble vascular cell adhesion molecule-1 (sVCAM-1), interferon gamma-induced protein 10 (IP-10), soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), and vascular endothelial growth factor (VEGF) which are independently associated with tau levels. [30] Brain lipids (ex. ceramides, cholesterol, and sulfatides) may also be good biomarkers in AD. [31, 32]

The potential of brain imaging for AD diagnosis has expanded rapidly with innovations in tools to acquire images and their analysis. We can now address structural, functional, and molecular aspects of the disease with imaging. Magnetic resonance imaging (MRI) is being used for both structural and functional and PET is for the evaluation of both amyloid and cerebral metabolisms. Clinically, patients with suspected AD will undergo a combination of the following imaging techniques: MRI, single photon emission computed tomography, and 18f Fluorodeoxyglucose-positron emission tomography (18F FDG PET). These imaging modalities allow healthcare providers to increase their confidence in an AD diagnosis if the patient shows the right pattern of brain involvement and related damage. These techniques can also help rule out other AD mimics. Other MRI techniques in development are diffusion tensor imaging (DTI) and associated tractography technologies, arterial spin labeling measures of cerebral blood flow, PET tracers targeted at the cholinergic system, microglial activation, and other tracers. Currently, these are used for research purposes and aren't approved for clinical diagnosis. [33-35]

Variations in glucose uptake patterns in the brain are scattered and delicate; so it's important to track metabolic changes to represent a subtle yet broad process. [36] The algorithm trains itself to identify metabolic patterns that correspond to Alzheimer's." [37] Computer software is intelligent enough to understand something as fine as glucose metabolism patterns and correlate it to more complex symptoms. One example of this was a test using Inception V3 image sorter, Unix commands, and Git Bash programming aid software, where volumetric reduction of the entorhinal cortex and hippocampal atrophy were the areas of differentiation between normal and AD patients. Another was Novel Machine Learning (MC), which identified subjects with both pre-MCI & MCI, (Mild Cognitive Impairment) and their progression into AD 3 years later.

Brain imaging, particularly MRI, differentiates Alzheimer's from other potential conditions, with the ability to show reduced hippocampal volume and medial temporal lobe atrophy, suggesting AD. MRI can predict how rapidly a disease will progress. FDG-PET and SPECT are functional imaging scans that specialize in showing brain activity. As a result of dying neuron connections, there is less activity in the brain, primarily the hippocampus, medial temporal lobe, mesial parietal lobes, posterior temporal, and lateral parietal lobes. In most atypical patients, Amyloid PET identifies amyloid plaque growths in the brain. While there is no single standard test for

diagnosis, the combination of patient history, MoCA testing, and imaging – particularly MRI, FDG-PET & potentially CSF – help make the diagnosis. [38, 39, 40]

Differential Diagnosis of Alzheimer's

Alzheimer's accounts for almost 80% of all cases of dementia, but there are several other types of variants with similar symptoms, so diagnosis can become complicated. Knowing the pathology and key features of each variant can increase accuracy in patient diagnosis, and so, differential diagnosis is made using imaging processes, initial symptoms, and neurology.

Neurodegeneration in Frontotemporal dementia (FTD) mainly affects the temporal and frontal brain lobes. Once considered rare, FTD is thought to now account for almost 10-15% of dementia cases and occurs primarily in 35-75-year-olds, earlier than Alzheimer's. Due to prominent personality and behavioral symptoms, it is often confused for a primary psychiatric disorder. FTD is often classified by personality and behavioral changes (lack of inhibition, uncharacteristic impulsiveness, inappropriate social conduct, disinterest in hygiene, and weight gain, even extending to illegal activities), and disruption in written/verbal expression (primary progressive aphasia) or comprehension issues (semantic dementia). There is no singular abnormality associated with all diseases in the FTD spectrum—hence the name, "dementia lacking distinct histopathologic features." Unlike AD, FTD patients initially present with neuropsychiatric symptoms such as lack of inhibition and inappropriate social conduct.

Lewy Body Dementia (LBD) is characterized by Lewy bodies—abnormal deposits of mostly alpha-synuclein protein—occurring in the brain in a wide spectrum of other neurodegenerative conditions. Cognitive pattern declines in LBD can involve visual hallucinations, confusion, poor judgment, and memory impairment. Cognitive symptom severity often fluctuates daily, including Parkinsonian motor symptoms ("mask-like" face, rigidity/stiffness, shuffling gait, and balance issues) with nearly ½ of all LBD patients suffering from rapid eye movement (REM) sleeping disorder, where normal muscle suppression in the REM sleep phase fails, resulting in violent & vivid dream enactment. In summary, LBD patients, unlike AD, will initially present with visual hallucinations, motor deficits, and sleep disturbances.

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive, one-in-a-million degenerative disorder. CJD and related conditions are "prion diseases"—naturally-occurring proteins in the brain, called prions, start to assume an "abnormal, three-dimensional shape" which spreads throughout the brain, killing and damaging cells. Cases are primarily sporadic, affecting individuals 60+, and while inheritable, the disease can also spread via infected tissue transplants/contaminated medical instruments. The disease may initially involve major cognitive domains—recent memory, language comprehension/expression, visuospatial ability (effective manipulation and comprehension of nonverbal information—mainly graphic or geographical) & executive function—impairment, depression, behavioral/personality changes, and agitation. Motor difficulties then may appear—namely involuntary muscle movement & akinetic mutism. While CJD patients may present similarly to AD patients, CJD patients will also often have motor symptoms such as myoclonus and depression, and anxiety at presentation along with distinct MRI findings.

Vascular Dementia is in the setting of vascular dysfunction, occurring when impaired circulation deprives brain cells of oxygen and food. Patients often present with sudden onset symptoms after a stroke, so stroke location and severity determine presentation. Often patients will have focal motor deficits along with memory and cognitive issues. MRI findings will show several cortical and subcortical infarcts. Patients usually have the criteria for other heart conditions (high BP, elevated lipids, vascular disease, stroke history, etc.) and many symptoms (ex. executive function) overlap with other conditions, as Vascular primarily occurs as mixed dementia. In summary, vascular dementia patients will present with stroke-like symptoms with a history/of stroke risk factors, and treatment will rely on addressing the underlying vascular issues.

The first symptom of AD is always memory loss—specifically, episodic memory loss. FD often results in apathy, poor judgment calls, and speech/comprehension disruption, and attacks language & frontal/executive function. (sparing drawing) LBD starts with visual hallucinations/delirium, Capgras' syndrome, and REM sleep disorder, (among others) and hits frontal/executive and drawing—sparing memory—resulting in more delirium-prone individuals. CJD begins with mood swings, anxiety, dementia, and movement disorders, and hits memory—frontal/executive, focal cortical, and variable. For Vascular Dementia, the first symptoms are not always—but often—sudden, and can include apathy, focal weakness, and slowing cognitive abilities. They end up hitting frontal/executive function, although they can spare memory.

On imaging scans, hippocampal and entorhinal cortex atrophy characterizes AD. [41] FTD is distinctive in its presentation of temporal, insular, and/or frontal atrophy—sparing the posterior parietal lobe. [42] LBD results in posterior parietal atrophy—with the hippocampus being larger in LBD than in AD. [43] Thalamus hyperintensity on FLAIR MRI [44, 45] and basal ganglia & cortical ribboning marks CJD. [46] Vascular Dementia primarily focuses on subcortical and/or cortical infarctions & confluent white matter hyperintensities. [47, 48]

Neuropsychiatry is the combined field of neurology and psychiatry and coupled with neurological exams, can help decide your definite diagnosis. In the initial stages of AD, neuropsychiatry and neurology exams appear normal. In FTD, the psychiatry test identifies disinhibition, apathy, depression, hyperorality, and euphoria, while neurology reports come in with the possibility of MND, axial rigidity, alien hand, dystonia, or vertical gaze palsy. [49, 50] In LBD, the most common features recognized in psychiatry tests are depression, delusions, sleep disorders, and (visual) hallucinations, while neurology reports identify Parkinsonism. [51] CJD displays anxiety and depression, as well as rigidity, myoclonus, and Parkinsonism. (in their respective test categories) [52, 53] The psychiatric test on Vascular Dementia shows anxiety, apathy, and delusions. Although the neurological exam may come back ordinary, chances are that the exam may also show spasticity — abnormal increases in muscle stiffness, prompting motor delay. [54-56]

Treatment of Alzheimer's with Imaging

Although symptomatic treatment targeting glutamatergic and cholinergic neurotransmission is available, there is no definitive cure for AD. [57, 58] Treatment protocols and regimens are patient-specific and the provider and patient must work together to determine the optimal dosing

and schedule. However, this often changes throughout the disease course. Pharmaceuticals are removed or added based on symptoms and patient quality of life decisions. Treatment of AD often utilizes two main drug/drug classes: memantine and cholinesterase inhibitors. Memantine—approved in 2003, for moderate to severe AD symptoms—is an NMDA receptor antagonist which reduces excitotoxicity (caused by excessive glutamatergic transmission) in Alzheimer's. Cholinesterase inhibitors—rivastigmine, donepezil, and galantamine—primarily target Cholinergic neurotransmission to improve cognition. [59-61] Additional drugs often given to AD patients include SNRIs and other antidepressants for mood-related symptoms and potential cholinergic effects. Recently, Aducanumab (Aduhelm™), which can help reduce and remove amyloid, was approved, although its efficacy has yet to be determined. [62]

Predicting treatment response is challenging, often taking years of trial and error to optimize patient drug regimens. Using AI to predict and build treatment protocols would save years of trial and error, increasing life expectancy and patient quality of life. AI integrates the accumulated imaging data and generates predictions for possible therapy options, increasing the probability of finding the best target and can process a vast amount of whole-genome data, to recognize the most relevant pathway. AI could answer more questions about memory decline, and tests are run to determine if AI could be used in clinical settings. AICS (Alzheimer's Intelligence Care System) is an example of an AI approach to predicting and assigning patient treatment protocols, with the approval of healthcare providers, by giving personalized treatment options based on MMSE (Mini-Mental State Examination) scores, providing patients with medicinal, nutritional, and athletic schedules to help patients keep track of their treatments and daily activities with inbuilt reminders. [63-65]

Conclusion

Alzheimer's disease, the most common form of dementia, is a progressive neurodegenerative condition with no definitive treatment currently. Beta-amyloid plaques and tau tangles are the most common neurological hallmarks, leading to brain atrophy. Risk factors include age, family genetics, Down syndrome, and head trauma. Diagnosis can be difficult, although imaging and cognitive testing, combined with thorough patient evaluation, help healthcare providers make the diagnosis. On MRI, patients with AD show atrophy of the hippocampus and entorhinal cortex. Amyloid PET can identify amyloid plaque in the brain in atypical patients. Other image technologies are being evaluated over potential utility in patient diagnosis. However, providers must include frontotemporal dementia, Lewy Body dementia, vascular dementia, and Creutzfeldt-Jakob disease on the differential. Treatment is expensive and often takes much trial and error to optimize treatment regimens. By processing whole genome data and other patient-specific markers, AI technologies can help predict and build treatment protocols, substantially increasing life expectancy and patient quality of life.

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