Molecular Imaging in Alzheimer's Disease

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Abstract

The most sensitive and accurate method for molecular imaging in human Alzheimer's disease (AD) is positron emission tomography (PET). The most widely available PET tracer, which is also used in clinical oncology, is 18F-2-fluoro-2-deoxy-D-glucose (FDG). FDG is an imaging biomarker for early and differential diagnosis of AD. Even higher molecular specificity and sensitivity for detection of AD before dementia onset is provided by high-affinity ligands for fibrillary amyloid. 11C-Pittsburgh Compound B is widely being used in research laboratories, while new 18F-labeled ligands are currently undergoing formal clinical trials as amyloid imaging agents and are expected to become commercially available for clinical use in the near future. A large variety of tracers is being developed and used in dementia research for activated microglia and multiple neurotransmitter systems to study disease pathophysiology, biological correlates of clinical symptoms, and new possibilities for treatment. Current studies in humans are investigating cholinergic, serotonergic, and dopaminergic neurotransmission.

Keywords

Alzheimer's disease (AD), dementia, positron emission tomography (PET), 18F-2-fluoro-2-deoxy-D-glucose (FDG), amyloid, microglia, acetylcholine, serotonin, dopamine

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Neurodegenerative dementia has become the most rapidly growing cause of severe disability in the world. The most important risk factor is old age, while genetics and lifestyle also contribute. Therefore, better treatment and effective intervention are urgently needed at an early stage before the onset of severe disability. This requires further research into the risk factors and pathophysiological determinants of disease manifestation in humans and better, specific diagnosis at an early stage before dementia develops. Molecular imaging can provide the tools to achieve these goals.

Positron Emission Tomography

The most sensitive and accurate method for molecular imaging in humans is positron emission tomography (PET) and therefore this article focuses on this technique. It employs minute amounts (in the micromolar range) of short-lived radioactive tracers. They are labeled with either:

- carbon-11 (physical half-life 20 minuntes), which requires a cyclotron and associated radiopharmacy on site and therefore is not practical for widespread clinical use; or
- fluorine-18 (half-life 90 minutes), which allows remote regional tracer production and delivery to clinical nuclear medicine departments.

Clinical PET scans typically involve intravenous tracer injection and subsequent brain scanning for 10–30 minutes at resting state. PET scans are associated with very low radiation exposure of approximately 5mSv.[1] This article discusses imaging biomarkers that are provided by clinical PET for early diagnosis of disease and monitoring of disease progression.[2,3] It describes the clinical utility of glucose and amyloid scanning. It also provides a brief overview of current research investigating possible determinants of disease progression, such as neuroinflammation, and changes in major neurotransmitter systems and their relation to clinical symptoms.

Amyloid Imaging

The deposition of amyloid-β (Aβ) is an early event in the pathogenesis of AD and is central in the amyloid cascade hypothesis. The first tracer to be used to label fibrillary Aβ selectively with high affinity *in vivo* was 11C-labelled Pittsburgh compound B (11C-PIB).[4,5] Many research studies and recent multicenter studies have demonstrated that this tracer has a very high sensitivity of 90% for detecting fibrillary amyloid plaques in patients with Alzheimer's disease (AD).[6–9]

The apolipoprotein E (APOE) e4 allele is a genetic risk factor for increased PIB uptake[10–12] and cortical PIB binding is correlated negatively with abeta42 in cerebrospinal fluid.[13–15] Similar results have been obtained with quantification of tracer binding by dynamic measurement and by simplified static imaging protocols recording cortical tracer uptake in a single scan lasting for 40 to 60 minutes following intravenous injection of

11C-PIB.[16,17] These results demonstrate the robustness and clinical applicability of the method. The cerebellar cortex, which may exhibit diffuse but not fibrillary amyloid in AD, is generally used as a reference region without specific PIB binding.

Most normal control subjects exhibit very low cortical binding of PIB, with less than 1.5-fold PIB uptake relative to the cerebellar cortex. In addition, unspecific binding is observed mainly in white matter. A proportion of normal elderly controls show higher cortical PIB binding, typically resulting in a bimodal distribution of PIB uptake in samples of control subjects. Current studies indicate that the frequency of increased cortical PIB binding in controls increases rapidly from 10% or less below 70 years of age to 30–40% at 80 years of age, largely reflecting similar findings in previous autopsy studies.[18] The clinical implications of Aβ deposition in elderly controls are not yet clear. Some elderly controls have indicators of the start of neurodegeneration[19,20] or will develop cognitive deficits,[21] but cerebral function in others may be resistant to Aβ deposition. Long-term follow-up studies are currently under way to clarify this issue.

Findings in patients with mild cognitive impairment (MCI) are heterogeneous. In most studies approximately two-thirds of patients showed increased binding, such as AD patients, while the rest were within normal limits. Published results from follow-up studies indicate that patients with increased binding are at high risk for progressing to AD with manifest dementia,[22,23] while MCI patients with negative PIB scans very rarely develop dementia.[24] Patients with amnestic MCI show more PIB binding than non-amnestic MCI.[25] Aβ deposition is high in posterior association areas, where it correlates with a decline in glucose metabolism. However, it is also high in the frontal association cortex where that correlation is absent.[26]

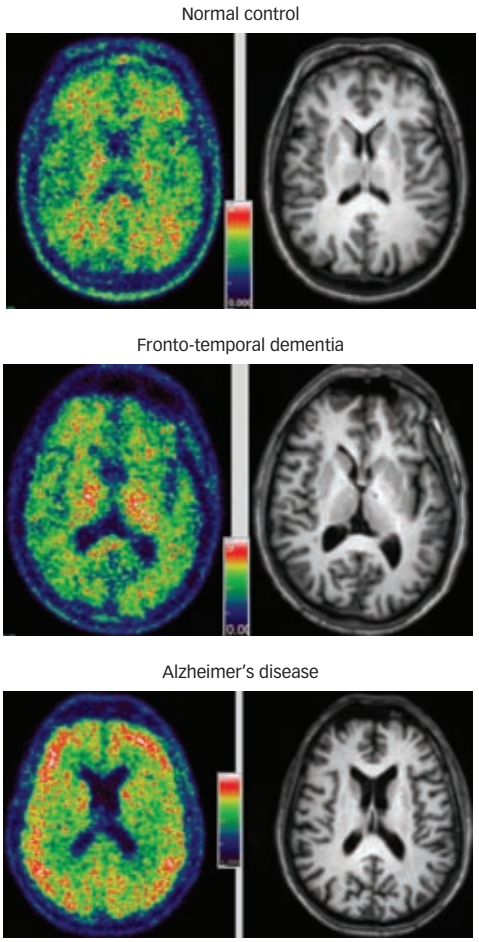
The amount of Aβ deposition and PIB binding is highly variable in AD. Despite this, PIB imaging is very sensitive for detection of AD. It is likely that a significant proportion of the PIB-negative AD patients in clinical series (up to 10%) will be due to clinical misdiagnoses. Only under exceptional circumstances has PIB-negativity been confirmed in AD.[27]

Besides APOE e4, additional genetic factors that have not yet been identified appear to play a role.[28] Initital follow-up studies with 11C-PIB in AD have indicated that there is little further increase in tracer uptake during progression of the disease.[29] However, recent preliminary results from large multicenter studies (ADNI and AIBL) do indicate further increase. A decrease in PIB binding has been observed in patients undergoing clinical trials of drugs that remove Aβ from the brain,[30] but it has not yet been demonstrated that this would be associated with clinical benefit.

Differential Diagnosis using Amyloid Imaging

Amyloid imaging is expected to provide excellent differentiation of AD from frontotemporal dementia, which is not associated with Aβ deposition and increased 11C-PIB binding (see *Figure 1*).[31] Dementia with Lewy bodies (DLB) often also shows fibrillary Aβ deposition in pathological studies and correspondingly positive PIB scans are reported in most patients.[32,33] Moderately increased PIB binding, predominantly in occipital regions and on average less than in AD, has also been observed in non-demented patients with cerebral Aβ angiopathy.[34]

Figure 1: Amyloid PET and MRI Brain Scans of Normal, Dementia, and Alzheimer's Disease Patients



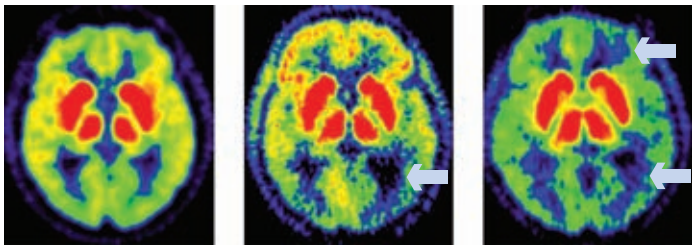
Amyloid positron emission tomography scans using florbetapir (with coregistered magnetic resonance imaging scans), demonstrating low normal cortical uptake in an aged normal control and a patient with fronto-temporal dementia in contrast to high cortical uptake in Alzheimer's disease.

Tracers in Clinical Trials

There are currently three 18F-labeled tracers being studied in clinical trials that have been developed as proprietary tracers for commercial distribution. These are flutemetamol (GE-067, 3'-fluoro-PIB), florbetaben (BAY-94-9172, AV-1), and florbetapir (AV-45). They show high-affinity binding for fibrillary Aβ with Ki <10nM, similar to 11C-PIB, while non-specific binding in white matter is higher than with 11C-PIB. Ongoing research is aiming to develop tracers that show a lower level of non-specific binding.[35,36]

Flutemetamol, florbetaben, and florbetapir appear to have largely similar imaging properties, although the optimum scanning time after intravenous injection varies. Results from clinical trials indicate that they will likely provide high diagnostic power for discrimination between AD patients and controls.[37,38] They also demonstrate a close correlation between the cortical binding of 11C-PIB and 18F-fluoro-PIB in cortical regions.[39] Preliminary results demonstrate a close correspondence of

Figure 2: Acetylcholine Esterase Activity in Alzheimer's Disease Compared with Dementia



Mild Alzheimer dementia MMSE 23 | Severe Alzheimer dementia MMSE 10 | Dementia with Lewey Bodies MMSE 19

Positron emission tomography scans of acetylcholine esterase activity (accumulation of 11C-MP4A 30 to 60 minutes after injection) in two patients with Alzheimer's disease showing reduction of cortical activity compared with more extensive reduction in dementia with Lewy bodies (arrows mark the brain areas with the most severe reduction).
MMSE = Mini Mental State Examination.

tracer binding with the amount of post-mortem Aβ deposition, as shown for florbetapir at the International Conference on Alzheimer's Disease (ICAD) 10 conference.[40]

Another F-18-labeled amyloid tracer is 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile, abbreviated to FDDNP, which binds to Aβ with less affinity than PIB and related compounds.[41] It competes with non-steroidal antiphlogistics[42] when binding and has significant affinity to pathological intracellular tau deposits (neurofibrillary tangles). These deposits are mainly located in the hippocampus in AD and also occur in other neurodegenerative diseases. Accordingly, a gradual increase in binding was observed in MCI and AD patients, mainly in the hippocampus but also in brain areas with predominant Aβ deposits.[43] Direct comparison with C-11-PIB demonstrated the differences in spatial distribution, and greater overlap between controls and patients than with C-11-PIB.[44,45]

Microglial Activation

Microglia are the resident immune cells of the brain. In response to brain damage, microglia undergo changes in their morphology, migrate toward the lesion site, proliferate, and produce cytokines and reactive oxygen species. This is associated with expression of the peripheral benzodiazepine receptor, which is known to be located at the mitochondrial translocator protein.[46] Activated microglia are present at sites of aggregated Aβ deposition in the brains of AD subjects[47] and may contribute to Aβ removal. However, the secretion of cytokines associated with microglial activation may also contribute to tissue damage and apoptosis. Further research with longitudinal assessment of microglial activation in humans is therefore needed to understand its consequences and whether it is a major factor that influences the rate of disease progression.[48]

Tracers for Microglial Activation Imaging

The first tracer that became available for imaging of microglial activation in humans was 11C-PK11195. This has been shown to largely reflect the distribution of activated microglia in experimental and human brain disease,[49,50] demonstrating microglial activation in multiple system atropy.[51] The *in vivo* PET findings in AD are not particularly clear. An early study using racemic 11C-PK11195 was negative,[52] probably due to the relatively high level of non-specific binding resulting in unfavorable signal strength. A recent study using the R-isomer according to current standards,[53] on the other hand, found moderately increased binding.

Thus, there is a need for the development of better tracers, ideally labeled with fluorine-18, for clinical use. A large number of new tracers have been tested in experimental animals.[54] Initial clinical studies using various tracers have detected that there is an as yet unidentified genetic polymorphism that leads very low binding with some of the new tracers in about one-fourth of normal individuals tested so far.[55,56] This complicates the clinical application of such tracers.

Glucose Metabolism

Cerebral glucose metabolism is measured by the most widely available PET tracer, 18F-2-fluoro-D-deoxyglucose (FDG). There is close coupling of glucose metabolism with neuronal function.[57] Glucose is the main substrate for the energy production that is required to maintain neuronal ion gradients for neuronal activity. Coupling to synaptic activity is also mediated by the neuron-astrocyte glutamate shuttle.[58,59]

Over more than 20 years, multiple studies have demonstrated that glucose metabolism and blood flow are imparied in temporal-parietal association cortices, with the angular gyrus usually being located at the center of the metabolic impairment.[60] The frontal association cortex may also be involved, but more variably so and usually to a lesser degree and only during progression of AD. There may be a distinct hemispheric asymmetry, which usually corresponds to the predominant cognitive deficits (language impairment in the dominant and visuospatial disorientation in the sub-dominant hemisphere).

In contrast to other dementia types, glucose metabolism in basal ganglia, primary motor, visual cortex, and cerebellum is usually well preserved. This pattern generally reflects the clinical symptoms of AD, with impairment of memory and associative thinking, including higher-order sensory processing and planning of action, but with relative preservation of primary motor and sensory function. Glucose metabolism provides high diagnostic power, especially when used in combination with automated objective image evaluation software.[61,62] As such, it has been recommended in current guidelines for dementia diagnosis.[63]

Longitudinal studies have demonstrated that the severity and extent of metabolic impairment in the temporal and parietal cortex increases with dementia progression and frontal reductions become more evident.[64,65] The annual decrease of metabolism in association cortices is 5–6%.[66,67] Asymmetrical metabolic impairment and associated predominance of language or visuospatial impairment tends to persist during progression.[68,69] Based on these observations, FDG PET can serve as a surrogate marker in therapeutic trials.[70–72]

There are several indications that increased activation in some parts of the brain may provide compensation for the failure of function in other parts.[73] During the pre-dementia stages of AD, frontal brain function may compensate for the failure of the Papez circuit—which includes the hippocampus and is essential for acquisition of long-term memory—as well as posterior association cortices. The prefrontal cortex was the

region with the most pronounced decline in brain metabolism in a study of progression from MCI to dementia.[74] Highly-educated patients beginning dementia appear able to partially compensate for impaired metabolism in the posterior cingulate cortex.[75] The very high frontal Aβ load in most patients before the onset of dementia is not paralleled by a decrease in glucose metabolism,[26] possibly indicating higher resistance of frontal neuronal function to pathological protein deposition.

Cholinergic Neurotransmission

It is known from pathological studies that there is a severe loss of cholinergic fibers and their characteristic enzymes and receptors in AD and DLB (see *Figure 2*).[76]

While there are no suitable tracers for acetylcholine transferase, tracers have been developed for other cholinergic markers. Labeled analogs of acetylcholine, which are also substrates for acetylcholine esterase (AChE), can be used to measure and image its activity *in vivo*. These acetylcholine analogs are 11C-N-methyl-4-piperidyl-acetate (MP4A, also known as AMP),[77] which is 94% specific for AChE in human brain, and 11C-N-methyl-4-piperidyl-propionate (MP4P or PMP).[78]

A significant decrease in cortical AChE activity has been observed in MCI and AD,[79] probably reflecting the loss of AChE that is associated with cholinergic axons.[80] The loss is most severe in the temporal neocortex, where it is correlated with memory deficits, while in other brain areas it is mostly related to deficits in attention.[81] The AChE imaging technique has also been used to measure drug-induced AChE inhibition in AD patients, which for all currently available cholinesterase inhibitors at standard clinical doses is in the range of 30–40%.[82–84]

Nicotinic receptors have attracted intense interest, but available tracers still suffer from methodological limitations. 11C-nicotine has a high level of unspecific binding, although reduced binding in AD can be detected.[85,86] The a4b2 receptor subtype has been imaged using 18F-A85380[87,88] and 131I-A85380.[89] Reduction of binding has been observed using these agents in MCI and AD,[90] as well as in Parkinson's disease with cognitive impairment.[91] Despite this, the binding kinetics are too slow for reliable quantitation and clinical use.[92] The quest for faster kinetics is motivating ongoing research for better ligands.

Serotonin

Impairment of serotonergic innervation has mostly been studied in the context of depression. Depression is also a major clinical issue in dementia. A reduction of receptor binding potential in AD has been observed in AD, mainly for 5-HT(2A) receptors.[93–95] In MCI, reduced 5-HT(2A) binding capacity in the striatum has been correlated with depression and anxiety scores.[96] Reduced serotonin transporter binding potentials have also been observed using 11C-DASB and is most clear in AD patients with depression.[97]

Dopamine

The tracer most widely used to examine dopamine synthesis and vesicular storage is 18F-fluorodopa.[98] A deficit of dopamine synthesis similar to Parkinson's disease has been found in DLB, even at a stage when parkinsonism may not yet be prominent.[99] As dopamine synthesis is normal in patients with AD, 18F-fluorodopa provides an important diagnostic marker. In contrast to the cholinergic impairment, which is severe in DLB but only mild in Parkinson's disease without dementia, the dopaminergic deficit does not appear to be related to dementia.[100] The dopaminergic degeneration in DLB is also evident in studies with ligands for dopamine transporters, such as 123I-FP-CIT.[101]

There is also interest in the imaging of vesicular monoamine transporters,[102] which provide a very sensitive—albeit probably somewhat less specific—indication of dopaminergic neurodegeneration.[103] Different transporter types have been compared in a multitracer study of the pathophysiology of dopamine turnover.[104]

Conclusion

Molecular imaging using PET in humans is providing powerful tools for specific and early diagnosis of AD even before the onset of dementia. There is a pressing need for the development of disease-modifying treatment that can prevent or delay dementia in patients who already carry the biological markers of AD but have little cognitive impairment. It is expected that molecular imaging will play an increasing role in reaching this goal by contributing to translational pathophysiological research, drug development and early clinical diagnosis. ■

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