Research Highlights

Highlights from the latest articles in imaging

In vivo mapping of amyloid toxicity in Alzheimer's disease

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Evaluation of: Frisoni GB, Lorenzi M, Caroli A, Kemppainen N, Någren K, Rinne JO: *In vivo* mapping of amyloid toxicity in Alzheimer disease. *Neurology* 72(17), 1504–1511 (2009).

It has generally been accepted that Alzheimer's disease is characterized by a direct correlation between the cognitive deterioration and cortical amyloid deposition, followed by brain atrophy. Consequently, a series of etiological therapies have been designed, pointing towards the inhibition or the reversal of amyloid deposition.

However, with the advent of ^{11}CPiB as a specific PET marker for amyloid, no definite connection between amyloid build-up and brain atrophy could be demonstrated. Postmortem studies have shown the presence of a better correlation between cortical atrophy and the degree of neurofibrillary entanglement.

The present study aims to clarify the relationship between gray matter atrophy (assessed with MRI) and amyloid deposition (using ^{11}CPiB-PET studies) in a study group including 23 patients diagnosed with Alzheimer's disease according to a worldwide-accepted criteria (Stroke-Alzheimer's Disease and Related Disorders Association) and 17 healthy volunteers.

All subjects underwent PET studies following the administration of 414 MBq ^{11}CPiB and an MRI scan. Images were processed according to standardized voxel-based procedures. Several Alzheimer's disease-relevant regions of interest were selected in the frontal and temporal lobes, posterior cingulated area, insula, acudate and amygdala. Subsequently, the two sets of images were correlated using a specifically designed statistical software.

Experimental results have demonstrated that amyloid deposition was not necessarily associated with an increased degree of gray matter atrophy, with the exception of the medial temporal lobe (hippocampus and amygdala). These findings suggest that amyloid deposition occurs only peripheral to neurodegeneration, and, furthermore, that the cognitive impairment is not necessarily primarily due to amyloid deposition.

The present study demonstrates the presence of a dissociation between neuronal loss and amyloid deposition, as indicated by the ^{11}CPiB uptake. The authors attribute these findings to two possible reasons:

- The hypothesis of a differential susceptibility, with regions with a higher task-related degree of activity being less sensitive to amyloid deposition while areas with a high degree of basal activity (posterior cingulate, temporoparietal and cingulate cortex) are potentially less resistant to amyloid deposition;
- Selective binding of ^{11}CPiB to different types of amyloid with various degrees of toxicity (extracellular amyloid vs vascular amyloid). This hypothesis remains to be tested, as the knowledge concerning the affinity of PiB to the various chemical variants of amyloid is incomplete.

The authors also identified several potential limitations of the study, including the mean age difference between the healthy volunteers and the patients with Alzheimer's disease, and the small size of regions of interest in certain areas, such as the hippocampus, which may have accounted for decreased signal owing to the inclusion of cerebrospinal fluid in the count

The results of the study are in agreement with a growing body of literature evidence that implies that amyloid

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deposition is not a causal but an adjacent factor to cerebral atrophy, as it has been demonstrated that older persons with no cognitive impairment can be positive for PiB fixation in the brain. In addition, several clinical trials have indicated that several anti-amyloid substances or vaccines have failed to prevent or delay the onset and evolution of Alzheimer's disease.

CAD system for neurodegenerative dementia using brain SPECT and 3D-SSP

Evaluation of: Ishii K, Kanda T, Uemura T *et al.*: CAD system for neurodegenerative dementia using brain SPECT and 3D-SSP. *Eur. J. Nucl. Med. Mol. Imaging* 36(5), 831–840 (2009).

The purpose of the study was to develop a computer-aided diagnosis system able to identify between various types of neurodegenerative disorders in patients with mild cognitive impairment due to Alzheimer's dementia (AD), dementia with Lewy bodies (DLB) and other causes.

MRI and PET studies have a proven value in the diagnosis of early-stage AD but their routine clinical use is limited owing to high cost and other practical considerations. The current study employs brain SPECT, which is a widely available low-cost procedure in most medical centers.

Based on their expertise using the NEUROSTAT system with ^{18}F-FDG-PET the authors have developed an automated diagnosis system using brain perfusion SPECT images following the administration of 111 MBq *N*-isopropyl-P-^{123}I-iodoamphetamine for distinguishing between AD/DLB and non-AD/DLB and for the differential diagnosis between AD and DLB for therapeutic purposes.

The study groups comprised AD/DLB patients and non-AD/DLB patients (fronto-temporal dementia) and progressive supranuclear palsy that fulfilled the international consensus criteria.

Initially, prototype regions-of-interest maps necessary for the stereotactic anatomic standardization were created, taking into account the individual size variations and regional anatomic differences, and the standard mapping. For each pixel of the region of interest, a Z score was calculated and threshold values were set. These numeric data were then used by the NEUROSTAT program for calculating the scores assigning the patients to the specific diagnostic groups.

Visual assessment of the SPECT images was also performed independently by two experienced radiologists and two unexperienced readers with no knowledge of clinical patient data. The criteria for diagnosis of AD were: decreased parieto-temporal perfusion, and obviously decreased perfusion in the posterior cingulated and/or precuneate areas, compared with the somatomotor areas. Brain SPECT images were visually categorized as definite AD, probable, improbable and indeterminate.

Computer-aided diagnosis results were compared with those of the visual readings. Computer-aided diagnosis demonstrated a sensitivity of 96%, a specificity of 70% and an accuracy of 93% for differentiating between the AD/DLB and non-AD/DLB groups. This very high accuracy is of clinical value in the differential diagnosis of early-stage AD and DLB. The authors demonstrated that the diagnostic ability of the 3D-SSP SPECT system was almost the same as that of experienced diagnostic radiologists.

In discriminating AD from DLB, automated diagnosis using brain SPECT had a lower accuracy of 69%, less than that reported previously for brain PET. In human observers, however, the degree of accuracy largely depends on the experience, as demonstrated in this paper, while the automated system is independent of observer skill.

The authors conclude that this completely automated system can be used for distinguishing AD/DLB from non-AD/DLB patients and has thus the potential of becoming a valuable tool for the clinician. Visual diagnosis, on the other hand, remains the task of expert imaging specialists.

Comparison of ^{18}F-FDG and PiB PET in cognitive impairment

Evaluation of: Lowe VJ, Kemp BJ, Jack CR Jr *et al.*: Comparison of ^{18}F-FDG and PiB PET in cognitive impairment. *J. Nucl. Med.* 50(6), 878–886 (2009).

Currently, one of the most important issues in patients with Alzheimer's dementia (AD) and other neurodegenerative-type dementias is assessing whether they respond to treatment and developing the most accurate tools for this purpose.

Patients with no cognitive impairment may evolve towards clinical AD, and patients diagnosed with mild cognitive impairment (MCI) may never convert to complete dementia. ^{18}F-FDG-PET has been demonstrated as a useful tool in the assessment of disease progression, being able to measure the decrease in the cortical metabolism. Lately an even more specific tracer, PiB, was developed. It is able to specifically bind to the amyloid plaques that are the mainstay of AD, thus aiding

not only in diagnosis of AD, but also in the assessment of the effects of anti-amyloid therapy trials.

Amyloid has been shown to accumulate in the brain of healthy elderly volunteers in a manner similar to AD but without the cognitive impairment. The study by Lowe *et al.* compares diagnostic performance of ^{18}F-FDG-PET and ^{11}C-PiB in order to distinguish between these two groups.

Diagnosis of the individuals included in the study population was made by consensus by a panel of experts comprising a nurse, psychometrist, neuropsychologist and neurologist using the Clinical Dementia Rating (CDR) score and the patient groups were categorized as no cognitive impairment, amnestic MCI (aMCI), nonamnestic MCI (naMCI) and positive mild AD.

Same day brain PET studies were performed following the injection of both ^{11}CPiB (average 600 MBq) and ^{18}F-FDG (average 540 MBq). For the automated labeling, several regions of interest (ROIs) were used (parietal, posterior cingulated, temporal, prefrontal, orbito-frontal, thalamus, striatum, primary sensory-motor, occipital, primary visual, cerebellum and pons). Ratios were calculated by dividing the median value of the given ROI to the median value of the control ROI, located in the cerebellum for PiB and in the pons for ^{18}F-FDG.

While PiB demonstrated a trend for improved accuracy compared with FDG, allowing for a better visual separation among the groups, data obtained with both PiB and ^{18}F-FDG were found to be complementary, accounting for a significantly improved discrimination between groups. PiB was also able to distinguish between patients with aMCI and naMCI.

The results of the study are of potential clinical significance since it has been shown that the aMCI group has a higher statistical risk of progressing to AD comparative to the low-risk naMCI group. It has also been hypothesized that amyloid deposition can be present without, or preceding, the cerebral metabolic disturbances, thus defining a risk group among the aMCI. Early amyloid deposition can be detected with a PiB PET scan of the brain, which may be used as a marker for the evolution toward AD even in the absence of any significant decrease in the cerebral metabolic rate, as measured with ^{18}F-FDG-PET.

FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease

Evaluation of: Mosconi L, Mistur R, Switalski R *et al.*: FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur. J. Nucl. Med. Mol. Imaging* 36(5), 811–822 (2009).

This study compares FDG-PET scans obtained in normal elderly persons and from patients with mild dementia of Alzheimer's type (DAT) in an attempt to develop markers for the preclinical early detection of neurodegenerative diseases, such as Alzheimer's disease. The study spanned an impressive period of more than 13 years and followed several elderly people from an asymptomatic period to the onset of clinical symptoms and used postmortem histopathological confirmation as the gold standard.

As there are several types of neurodegenerative disease with similar clinical aspects, the final confirmation of Alzheimer's disease is currently made mainly by postmortem histological examinations of the hippocampus, demonstrating the pathognomonic Alzheimer's plaques or neurofibrillary tangles (NFTs).

The cerebral metabolic rate for glucose (CMRglc) is a PET marker for Alzheimer's disease staging. Its reduction in the parieto-temporal, posterior cingulated, and medial temporal and frontal areas is directly proportional with the severity of the disease. Reduced CMRglc in the hippocampus may indicate the transition from normal cognition to mild cognitive impairment (MCI) and from MCI to dementia.

The study followed voluntary subjects over a period of more than 13 years, who were assessed at regular intervals, including evaluation of their medical, neurological, neuropsychological and mental status. Presence of any conditions affecting brain structure and function (e.g., diabetes, stroke, trauma and depression of medication) were reasons for exclusion from the study. The final study population included seven patients, four of which were considered normal and three with baseline diagnosis of DAT.

After death, the brain was weighed, the left parts of the cortex, midbrain, brainstem and cerebellum were fixated with buffered

formalin and the equivalent right sides were frozen then sliced. Amyloid-β and NFT burdens were assessed according to the CERAD and Braak and Braak criteria.

All subjects underwent PET of the brain following the injection of 200–320 MBq ^{18}FDG and the CMRglc was calculated (μmol/kg/min). MRI scans were used for the exclusion of hydrocephalus, intracranial masses, stroke and white matter disease.

FDG-PET image analysis was performed using the NEUROSTAT Statistical Image Analysis Package. Automated regions of interest were used to sample the CMRglc from the specific Alzheimer's disease-related brain regions (e.g., hippocampus, inferior parietal lobe, lateral temporal lobe and prefrontal cortex).

A statistically significant correlation was found between the progression of a decrease in the CMRglc and the decline of cognition to the appearance of MCI and DAT up until the postmortem verification.

The decrease in CMRglc preceded the onset of clinical symptoms by many years and correlated with the severity of dementia. A hippocampal reduction in the CMRglc preceded the appearance of the symptoms while cortical reduction of metabolism was almost simultaneous with the appearance of symptomatology.

These findings are in agreement with previous observations of a relationship between a decrease in CMRglc and cerebral blood flow and regional densities of NFTs. FDG-PET findings were useful in detecting pathological features that were not clinically obvious, such as indicating the presence of Lewy body dementia that was confirmed postmortem. Reduction in CMRglc, measured prior to the onset of dementia, progresses in parallel with the severity of Alzheimer's disease. These results suggest that quantitative brain FDG-PET with measurement of CMRglc is a clinical tool that can be used in both detecting and staging preclinical Alzheimer's disease.