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Review

Molecular imaging of dementia

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ABSTRACT

The increasing age of the population due to improvements in health care in the past century contributes to an increase in the number of people with dementia. However, with an appropriate support and symptomatic treatment, many patients can continue to have an active life and a good quality of life. Treatment and support work best if they are applied at an early stage and also new disease modifying treatments need to focus on predementia and presymptomatic stages of disease.

This article focuses on the role of molecular neuroimaging biomarkers in the reliable clinical diagnosis of dementia at the earliest possible stage of different forms of dementia like Alzheimer's disease, Dementia with Lewy Bodies and frontotemporal lobar degeneration. These different types of dementia are associated with characteristic patterns of hypometabolism in F-18-FDG PET. These reductions occur already years before the onset of symptoms and are strongly correlated with clinical severity.

Recently developed Amyloid-PET-tracers hold promises to be efficient tools in the near future to depict the earliest stages of AD. They may also serve to directly monitor changes of amyloid load due to new treatment approaches.

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1. Introduction

Current demographic trends show a rise in age-associated neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Dementia can also occur below the age of 60; typically this occurs in Parkinson's disease and frontotemporal lobar degeneration, but also in some cases of Alzheimer's disease. A recent meta-analysis by Prince et al. (2013) estimated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. This will result in a major economic challenge for health care in the future. In 2010 the total estimated worldwide costs of dementia were US$ 604 billion and about 70% of the costs occurred in Western Europe and North America (Wimo et al., 2013). The CDBE2010 study group and the European Brain Council found that in 2010 the total annual cost for diagnosis, therapy and care of patients suffering from dementia in Europe was € 105.2 billion (Olesen et al., 2012). Currently no approved disease-modifying therapies are available, although numerous new therapies are being investigated in various stages of clinical trials. On the other hand there is much that can be offered

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to support and improve the lives of patients with dementia and their caregivers and families, including symptomatic treatment with antidementive drugs, cognitive intervention to preserve the global cognitive status (Buschert et al., 2012) and caregiver counseling. Treatment and support work best if they are applied early in the disease course. Therefore one of the key objectives for the care of patients suffering from dementia is early clinical diagnosis. In addition, research on disease modifying treatments needs to focus on predementia and presymptomatic stages of disease when processes of neurodegeneration may still be partly reversible. Therefore, diagnostic markers are required that detect the underlying neurobiological changes of disease prior to the manifestation of symptoms to select at risk subjects for future disease modifying and preventive treatment trials.

The need of early clinical and predementia diagnosis has driven international efforts to define new diagnostic entities of Alzheimer's disease based on biomarkers (Genius et al., 2012). Biomarkers are pathological, physiological or anatomical parameters, which indicate biological and pathological processes or allow the evaluation of therapeutic interventions. In a clinical context, biomarkers can be both imaging techniques (e.g. PET, SPECT and MRI) as well as the concentration of certain proteins in the cerebrospinal fluid (e.g. tau protein and beta-amyloid (A42)). Their use is essential for the diagnosis of neurodegenerative diseases in addition to the clinical manifestation because different neuropathological changes lead to similar clinical symptoms and vice versa, and different clinical symptoms are based on the same neuropathological changes. For example, Shaffer et al. noted that the rate of misdiagnosis in very early stages of Alzheimer's disease can be as great as 41.3%. By combining different biomarkers with clinical tests, they were able to reduce the frequency of misdiagnoses to 28.4% (Shaffer et al., 2013). The use of molecular imaging by PET or SPECT as biomarkers plays an important role in the differential diagnosis of neurodegenerative diseases. Based on available studies, indications for molecular imaging, especially for PET, in the differential diagnosis of three main types of dementia will be presented in the following: Alzheimer's disease (AD), dementia with Lewy bodies, Parkinson's dementia and frontotemporal lobar degenerations (FTLD).

2. Fundamentals of PET and PET/CT for brain imaging

In the past decade positron emission tomography (PET) has become a well-established imaging modality and standard procedure in both oncology and neurology. Positron emission tomography uses positron emitter labeled radiopharmaceuticals, which interact with specific cellular targets after injection. The radionuclide is subject to physical decay and thereby releases positrons. An emitted positron travels a small distance in the surrounding tissue (approx. 1 mm), losing energy until it annihilates with an electron resulting in the simultaneous emission of two photons with 511 keV each at an angle of 180° to each other. The image reconstruction is based on the detection of the two annihilating photons by two detectors located exactly opposite to each other within a short time window. A multitude of such pairs of detectors surrounds the patient, each defining a line-of-response along which the emission point of the two annihilation photons is located, Fig. 1. The measured coincidences are usually stored in sinograms, containing the projections over all angles of the distribution of the radiopharmaceutical in the patient. Reconstruction of the 3D activity distribution from these measured sinograms includes corrections for scatter, randoms, attenuation, dead time and normalization, making PET a quantitative technique. The combination of PET and computer tomography (CT) into one device (PET/CT) allows the use of PET and CT diagnostics during one single study. PET provides information on metabolism, at the same time CT depicts exquisite anatomical details and enables a highly accurate attenuation correction for the PET data.

Fluorine-18 labeled fluorodeoxyglucose (F-18-FDG) is the most commonly used radiopharmaceutical for PET brain imaging. F-18-FDG passes the blood–brain-barrier, is taken up into neuroglia by glucose transporters and then phosphorylated to F-18-FDG-6-phosphate by the enzyme hexokinase. F-18-FDG-6-phosphate is not further metabolized within the cells. Since dephosphatase is down regulated, a dephosphorylation does not occur and as a consequence F-18-FDG-6-phosphate is trapped in the cellular compartment. The FDG uptake in the brain reflects local glucose consumption and as it is directly linked to the synthesis of glutamate and its recycling via the neuroglia (Magistretti and Pellerin, 1999; Sokoloff, 1960) it is closely coupled with neuronal function at rest and during activation, see Fig. 2. F-18-FDG-PET images are typically obtained 30–60 min after tracer injection, with measurement times that can be as short as 5–10 min. Appropriate PET imaging requires well-controlled standard conditions to avoid confounding of scans by uncontrolled brain activation (Herholz et al., 2007).

Neuronal degeneration regularly leads to a reduced glucose metabolism in the affected brain areas. Almost all neurodegenerative diseases have very distinct predilection sites in the brain that are primarily affected, whereas other parts of the brain are spared at least in the early stages. This leads to characteristic topographical patterns of cortical glucose consumption that provide

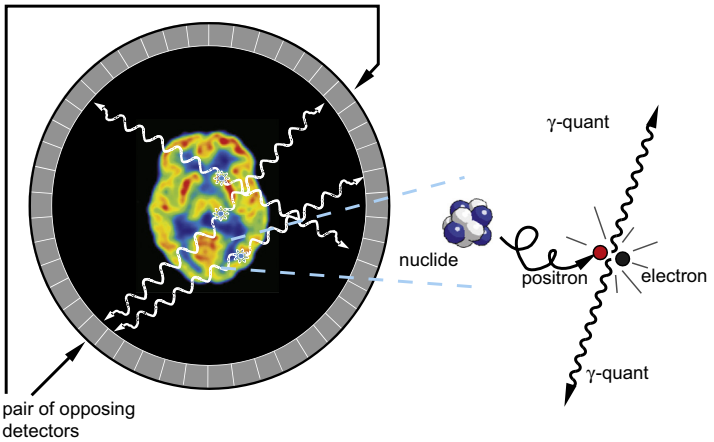

Fig. 1. Principle of PET technique: the administered radiopharmaceutical emits a positron, which travels in tissue for a short distance, interacts with an electron and annihilates both electron and positron, producing a pair of photons moving in opposite directions. Pairs of surrounding scintillators detect these photons coincidently. Millions of these coincidence detections are acquired during a PET scan.