2b

Role of FDG-PET

P. Bartenstein (Mainz)

The most frequent clinical application of functional brain imaging is currently PET with FDG in neurodegenerative dementia. Especially in the early detection of dementia of Alzheimer type (DAT), which is by far the most frequent dementing disorder (70 % of all dementing disorders), there is no other non-invasive diagnostic tool with similar accuracy (1, 2). FDG-PET allows for the diagnosis of DAT through the detection of impaired glucose metabolism in regions, which are primarily affected by histopathological changes typical for this disorder. The local impairment of glucose metabolism generates characteristic patterns, which in the case of bilateral temporoparietal hypometabolism present in most patients, are very specific (specificities and sensitivities >95 % are reported even in large patient samples usually with clinical criteria as gold standard (e.g. 3). It was possible to prove the high diagnostic accuracy of these patterns (at least for SPECT) on a large patient sample, where post mortem verification of the diagnosis was possible (4). Standardized observer-independent analytical approaches, which were developed specifically for this purpose and evaluated in large patient cohorts allow nowadays for a very good reproducibility of diagnostic findings even for less experienced observers and a very good comparability between different sites (eg. 1,4).

A number of publications produced evidence, that FDG-PET is more sensitive than measurements of regional cerebral blood flow with SPECT especially in early stages of Alzheimer´s disease, although generally the occurrence of local changes in perfusion and glucose metabolism is congruent. The detection of cortical atrophy with CT is a unreliable sign for DAT and in addition not sufficiently sensitive. The detection of hippocampal atrophy with MR and CT allows for the discrimination between patients with moderate and severe DAT and age matched controls. Although larger comparative studies are missing available publications suggest a lower sensitivity of these investigations in early stages of the disease compared to FDG-PET. Probably due to cost limitations a prospective study investigating the predictive value with FDG-PET for the development of DAT in a larger sample of still asymptomatic persons has not been performed yet. A number of publications however was able to provide evidence in smaller populations, that characteristic abnormalities in FDG-PET are detectable more than one year before the clinical diagnosis of DAT can be established according to NINCDS-ADRDA criteria (eg.1, 2). A study performed by Reiman et al. (5) was able to demonstrate impressively, that FDG-PET is able to detect in patients with high genetic risk for DAT the typical patterns of abnormal glucose metabolism before any clinical symptoms occur. This high sensitivity makes the clinical use of FDG-PET an especially valuable tool to predict the conversion of patients with mild cognitive impairment (MCI) to clinical DAT. Several groups were able to demonstrate that reduced glucose metabolism in posterior cingulate is hereby the most reliable sign (eg. 1).

Since the use of FDG-PET allows for a confirmation of the diagnosis in very early stages of Alzheimer´s disease, when clinically no clear evidence of dementia is present, this diagnostic approach provides the opportunity to initiate an adequate therapeutic strategy before major cognitive decline occures. Since FDG uptake can be regarded as a surrogate marker for neuronal activity FDG-PET is also suitable to control short-term and long-term effects of drug therapy (6). If the latter application however will gain clinical importance beyond drug trials is dubious considering the costs of repeated PET measurements.

The high diagnostic accuracy of the above described patterns of impaired glucose metabolism allows for a reliable differentiation between DAT and functional cognitive impairment, apparent eg. in depressive pseudodementia. In this clinically often difficult differential diagnosis FDG-PET can provide information which has immediate therapeutic consequences. Typical patterns of impaired glucose utilisation can also be observed in very early cases of frontotemporal dementia and in degenerative disorders of the striatum like Huntington´s disease and the multiple system atrophies. These changes are (in equivalence to the situation in DAT) tightly correlated to the histopathological changes.

Difficulties in differential diagnosis with FDG-PET can be observed in the distinction between DAT and Lewy-Body dementia (DLB), which is prevalent in autopsy samples in 13-26 % of all dementing disorders. Ante mortem this disease is considerably less often diagnosed . The analysis of FDG-PET images

with standardized observer independent approaches allows to some extent the non-invasive differentiation between DLB and DAT. Minoshima et al. (7) were able to distinguish in an autopsy validated study DLB and DAT with 90 % sensitivity and 80 % specificity. The most reliable factor distinguishing both disease entities was the impaired glucose utilisation in the occipital cortex in DLB, especially in the primary visual cortex.

Imaging with radiopharmaceuticals targeting amyloid plaques in DAT has the fascinating advantage compared to FDG that it provides positive proof of the presence of disease. But before this procedure is established in the clinical setting verification is needed, that the diagnostic accuracy of amyloid imaging is superior to FDG-PET.

References

1. Drzezga A, Lautenschlager N, Siebner H, et al. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur J Nucl Med Mol Imaging 2003;30:1104-13
2. Scheurich A, Müller MJ, Siessmeier T, et al. Validating the DemTect with 18-Fluoro-2-Deoxy-Glucose Positron Emission Tomography as a Sensitive Neuropsychological Screening Test for Early Alzheimer Disease in Patients of a Memory Clinic. Dement Geriatr Cogn Disord 2005; 20: 271-77
3. Herholz K, Perani D, Salmon E, et al. Comparability of FDG PET studies in probable Alzheimer's disease. J Nucl Med 1993; 34: 1460-6
4. Jobst KA, Hindley NJ, King E, Smith AD. The diagnosis of Alzheimer´s disease: a question of image? J Clin Psychiatry 1994; 55 suppl: 22-31
5. Minoshima S, Foster NL, Sima AA, et al. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol. 2001;50: 358-65
6. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer´s disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med 1996; 334: 752-8
7. Nordberg A. Functional studies of new drugs for the treatment of Alzheimer´s disease. Acta Neurol Scand 1996 suppl 165: 137-44