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Clinical severity of Alzheimer's disease is associated with PIB uptake in PET☆

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Abstract

Background: The positron emission tomography (PET) tracer [11C]-Pittsburgh Compound-B ([11C]PIB) allows the in vivo assessment of amyloid plaque burden in the brain. In a cross-sectional study we examined the association between the severity of dementia assessed using the Clinical Dementia Rating scale sum of boxes (CDR-SOB) and [11C]PIB-PET in patients with Alzheimer's disease (AD).

Methods: Patients with probable AD who had an AD-typical [18F]FDG-PET scan were included. Linear regression analysis in anatomically defined regions-of-interest (ROIs) and correlation analysis using statistical parametric mapping (SPM) were used to determine the association between CDR-SOB and [11C]PIB uptake.

Results: The linear regression analyses showed that the CDR-SOB explained approximately 11–22% of the variance of [11C]PIB uptake. The association attained statistical significance in both frontal, in both anterior cingulate cortices, and in both putamina. The SPM analysis showed a significant association in more widespread regions of the brain, with maxima located in similar areas as in the ROI-analysis.

Conclusion: The CDR-SOB score is significantly associated with [11C]PIB uptake in patients with AD. Thus [11C]PIB is a potential surrogate marker of dementia severity.

Keywords: Alzheimer's disease; Dementia; Clinical Dementia Rating; Amyloid plaques; Positron emission tomography; Imaging; [18F]FDG; [11C]PIB; Pittsburgh Compound B

1. Introduction

The increased generation of Aβ-amyloid peptides and their deposition in the form of plaques is currently regarded as one of the major events within the pathological cascade of Alzheimer's disease (AD) (Hardy and Selkoe, 2002). Still today the exact pathomechanism linking amyloid deposits to the clinical symptoms of AD is not clear. It has been discussed that soluble amyloid oligomers may be mainly responsible for progressive synaptic and neuritic injury, while amyloid deposits could be relatively inert.

There is controversy, however, to which extent amyloid deposition is related to clinical symptoms. Some authors have

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found a strong correlation between amyloid plaque density in the brain and overall clinical severity (Cummings et al., 1996; Fernández-Vizarra et al., 2004; Gold et al., 2001; Haroutunian et al., 1998; McKeel et al., 2004). Others have argued that plaque density is less tightly correlated to the clinical expression of the disease than neurofibrillary tangle density (Berg et al., 1998; Prohovnik et al., 2006; Tiraboschi et al., 2004), that the strength of the association decreases in patients older than 85 years (Prohovnik et al., 2006), that measures of Aβ42 and Aβ40 but not plaque deposition are correlated with the severity of dementia (Näßlund et al., 2000), and that only the number of cored plaques is increased in patients at a more severe stage of AD whereas the amount of diffuse plaques is less related to disease stage (Berg et al., 1998).

The advent of new positron emission tomography (PET) tracers for amyloid plaque imaging including the naphthylethylidene-derivative [18F]FDDNP and the thioflavine-T-derivative [11C]6-0H-BTA-1, also referred to as Pittsburgh Compound-B (PIB), has enabled researchers to assess the relationship between amyloid plaque load and clinical severity in the living patient at various clinical stages. Initial studies using these tracers have shown that amyloid deposition is increased in patients with AD relative to healthy age-matched controls in several cortical areas including the temporo-parietal and frontal cortex (Klunk et al., 2004; Shoghi-Jadid et al., 2002). Moreover, there is preliminary evidence that [11C]PIB tracer uptake is greater in AD than in non-amyloid neurodegenerations (Drzezga et al., 2008). The potential of amyloid imaging for early and differential diagnosis, however, has not been fully explored to date. The in vivo assessment of brain amyloid burden may be a valuable tool for treatment monitoring and evaluation, which is of particular interest with regard to upcoming disease-modifying treatments such as immunotherapy which target at amyloid pathology (Bayer et al., 2005; Gilman et al., 2005). The amyloid plaque tracer [11C]PIB has been shown to bind to different forms of amyloid plaques, including cored ("senile") plaques which become more abundant in the severe stages of AD (Lockhart et al., 2007). Therefore, some quantitative association of tracer uptake with measures of clinical expression may be expected. Recent studies, however, which have looked at the relationship of [11-C]PIB-uptake in AD patients with clinical measures have revealed controversial results. An association between the Mini Mental State Examination (MMSE) score (Folstein et al., 1975) and overall [11C]PIB uptake in the cortex was not observed in a recent cross-sectional study on 17 patients with mild to moderate AD (Rowe et al., 2007). On the other hand, a 2-year longitudinal study using [11C]PIB in patients with AD demonstrated a significant correlation between the MMSE and [11C]PIB uptake in the frontal, parietal, and occipital cortex at baseline, but no significant increase in [11C]PIB retention over time (Engler et al., 2006). Furthermore, in patients with mild cognitive impairment (MCI), which frequently represents a pre-dementia stage of AD, a significant correlation between episodic memory impairment and [11-C]PIB uptake has been shown (Forsberg et al., 2007).

The aim of the current study was to examine the association between the severity of dementia assessed with the Clinical Dementia Rating scale sum of boxes (CDR-SOB) (Morris et al., 1989) and brain amyloid plaque load as measured using [11-C]PIB-PET. The association was examined using two different statistical approaches (1) linear regression analysis including the CDR-SOB score and tracer uptake in anatomically defined regions of interest, and (2) voxel-based statistical parametric mapping.

2. Methods

2.1. Patient recruitment, inclusion and exclusion criteria

Patients were recruited from the research outpatient unit for cognitive disorders at the department of psychiatry, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Munich, Germany. They had been referred for the diagnostic evaluation of cognitive impairment by general practitioners, neurologists, psychiatrists, or other institutions, and underwent a standardized diagnostic procedure. The study protocol was approved by the local ethics committee and by radiation protection authorities.

The diagnostic work-up included an interview with the patient and an informant, medical, psychiatric and neurological examinations, neuropsychological testing, a routine laboratory screen, and apolipoprotein E (ApoE) genotyping. Cranial magnetic resonance imaging (MRI) was performed to assess structural brain abnormalities. Cranial [18F]Fluoro-deoxy-glucose positron emission tomography (FDG PET) was used to determine cerebral metabolism, and [11C]PIB-PET was used to assess amyloid plaque burden.

All study participants met NINCDS-ARDRA diagnostic criteria for probable AD (McKhann et al., 1984). Patients with mild to moderate dementia were included. Furthermore, FDG PET findings typical for AD were required, i.e. hypometabolism in the temporo-parietal and posterior cingulate cortex with relative sparing of the primary sensomotor cortex (Minoshima, 2003).

The diagnostic evaluation of FDG PET images was performed by an experienced nuclear medicine specialist.

Patients were not included in the study if they met diagnostic criteria for other neurological or psychiatric disorders, including Parkinson's disease, normal pressure hydrocephalus, progressive nuclear palsy, or major depression. Patients were also excluded if they showed any major abnormalities on MRI, such as brain infarcts, extensive leucoencephalopathy, intracerebral aneurysm, or arteriovenous malformation. NINDS–AIREN criteria were used to exclude vascular dementia (Roman et al., 1993). Furthermore, patients with other possible causes of neuropsychological impairment such as psychotropic medication (e.g.