Evaluating Atypical Dementia Syndromes Using Positron Emission Tomography With Carbon 11–Labeled Pittsburgh Compound B

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Context: A progressive decline in episodic memory affecting activities of daily living is the usual clinical presentation of Alzheimer disease. However, patients presenting with atypical or focal clinical symptoms such as language or visuospatial dysfunction often pose a diagnostic challenge.

Objective: To explore the presence and topography of β amyloid (Aβ) as measured by carbon 11–labeled Pittsburgh Compound B (11C-PiB) in patients with atypical presentations of dementia.

Design, Setting, and Participants: At a tertiary referral center for memory disorders, 15 healthy controls, 10 patients with Alzheimer disease, a patient with primary progressive aphasia (PPA), and a patient with posterior cortical atrophy (PCA) underwent 11C-PiB positron emission tomographic studies. Retention of 11C-PiB was compared between different groups using statistical parametric mapping.

Main Outcome Measure: The topography of cortical 11C-PiB binding in atypical vs typical Alzheimer disease.

Results: Cortical 11C-PiB binding was higher in the group with Alzheimer disease and in the patients with PPA and PCA than the controls (P < .001). Both patients with atypical dementia had a similar 11C-PiB binding pattern to Alzheimer disease although 11C-PiB retention was higher on the left cerebral hemisphere in the patient with PPA (P < .01) and higher in the occipital cortex in the patient with PCA (P < .01).

Conclusions: The presence of distinctive focal 11C-PiB retention patterns was demonstrated in 2 patients with atypical onset of dementia. Pittsburgh Compound B has the potential to facilitate differential diagnosis of dementia and identify patients who could benefit from specific therapeutic strategies aimed at β amyloid reduction.

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While the majority of patients with Alzheimer disease (AD) have prominent memory impairment early in the course of the disease, 15% of all patients with AD present with focal syndromes that initially spare memory, attention, executive function, and insight. Patients with atypical AD tend to have a younger age at onset and a more protracted disease course. Five different types of atypical AD presentations have been described: progressive aphasia; posterior cortical atrophy (PCA); and visual-, frontal-, and extra-pyramidal-variant AD. The criteria from the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association for AD are weighted heavily on the memory domain of cognition, which may preclude the early diagnosis of atypical cases.

Primary progressive aphasia (PPA) is currently classified as a subtype of frontotemporal dementia and is diagnosed when a patient suffers from language dysfunction for the first 2 years of the disease course, sparing other aspects of cognition. Primary progressive aphasia includes fluent and nonfluent types with the latter being more common. There is considerable heterogeneity in the pathology of PPA: 60% show nonspecific features such as gliosis and spongiform changes; 20% show β amyloid (Aβ) plaques and neurofibrillary tangles; and 20% show Pick bodies. Neurodegenerative changes have been localized to the frontal and left perisylvian temporal cortex with supporting data from structural and functional neuroimaging studies.

Posterior cortical atrophy (PCA) is a neurodegenerative disorder of the posterior cerebral cortex, a highly specialized area responsible for higher-order visual processing and spatial praxis.
cortical atrophy is clinically characterized by features of Balint syndrome (ocular apraxia, optic ataxia, and simultanagnosia). Other clinical features include visual agnosia, constructional and dressing apraxia, ideomotor apraxia, prosopagnosia, and left hemineglect. Most reported cases of PCA have AD pathology with visual and posterior parietal cortex showing double the concentration of Aβ plaques and neurofibrillary tangles than would be seen in typical AD. Magnetic resonance imaging (MRI) may show predominantly right-sided parietal and occipital cortical atrophy. The purpose of this study was to explore the presence and topography of 11C-PiB retention in 2 patients, one diagnosed clinically as PCA and the other as PCA, and compare them against age-matched controls and patients with typical AD using voxel-based image analysis.

## METHODS

Fifteen elderly individuals with normal cognitive function and 12 patients with well-characterized dementia (10 AD, 1 PPA, 1 PCA) were included in this study. All studies were approved by the Austin Health research ethics committee, and informed consent was obtained from all subjects. Demographic characteristics are summarized in the Table. 

### CASE HISTORY 1: PRIMARY PROGRESSIVE APHASIA

In 2002, a 79-year-old man presented with 6 years of word-finding difficulties. Initial assessment revealed mild dysnomia and confrontation naming sparing other aspects of cognition. Repeat evaluation in 2005 revealed significant word-retrieval difficulties and the occasional phonological paraphasic error. There were significant difficulties with spelling and reading and subtle reduction in semantic processing. His logical grammatical comprehension was intact. Working memory and attention independent of language were only mildly impaired. His visuospatial processing ability was intact, insight was preserved, and there were no behavioral symptoms of frontotemporal dementia. His MRI demonstrated left-sided perisylvian cortical atrophy accompanied by hypometabolism on 18F-FDG PET (Figure 1).

### CASE HISTORY 2: POSTERIOR CORtical ATROPHY

In 2003, a 64-year-old woman presented with progressive visuospatial difficulties and left-arm apraxia over 3 years. Her short-term memory and insight were relatively preserved until 2005. Physical examination confirmed left-sided visual neglect, and motor apraxia (both dressing and constructional). Oculomotor apraxia, optic ataxia, and simultanagnosia were evident. There were no other focal neurological deficits or apparent extrapyramidal features. Magnetic resonance imaging demonstrated severe parietal cortical atrophy (Figure 2A), and 18F-FDG PET (Figure 2B) showed profound hypometabolism in the parietal and visual cortices.

### NEUROIMAGING

All subjects underwent a T1-weighted spoiled gradient echo sequence MRI for subsequent coregistration with the PET images. T2-weighted and fluid-attenuated inversion recovery sequences were performed to rule out stroke. Each subject received 375 ± 18 MBq 11C-PiB by intravenous injection at the beginning of a 90-minute dynamic PET acquisition. Decay-corrected PET data were standardized for injected dose and individual body weight to generate standardized uptake values. The data acquired between 40 and 70 minutes postinjection were summed and normalized to the cerebellar cortex to generate standardized uptake value ratio (SUVR40-70) images. The cerebellar cortex, being devoid of neuritic amyloid plaques, is used commonly as a reference tissue in 11C-PiB quantification.

### STATISTICAL PARAMETRIC MAPPING ANALYSIS

The SUVR40-70 PET images were coregistered to individual MRIs using statistical parametric mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, England) and subsequently spatially normalized to the Montreal Brain template (Montreal Neurological Institute, Montreal, Quebec) to remove intersubject anatomical variability. The voxel-based statistical parametric mapping between-group comparisons using a 2-sample t test were performed without any a priori
The between-group statistical parametric mapping analysis showed that 11C-PiB retention in patients with typical AD was higher than control subjects in the orbitofrontal, posterior cingulate, temporal, and parietal cortex with relative sparing of medial temporal, sensorimotor, and occipital cortex (Figure 3). The most significant clusters were found in the posterior cingulate, orbitofrontal, and parietal cortex. Both the patient with PPA and the patient with PCA had 11C-PiB retention patterns resembling AD when between-group analysis was performed against the controls. When compared with subjects with typical AD, the patient with PPA showed asymmetric focal 11C-PiB retention of the left frontotemporal cortex (Figure 4) and the patient with PCA had visual cortical 11C-PiB retention in contrast to the occipital sparing seen in AD (Figure 4).
Figure 3. Visualization of the results of statistical parametric mapping analysis. The regions with statistically significant increases ($P < .001$) in retention of carbon 11-labeled Pittsburgh Compound B ($^{11}$C-PiB) in patients with Alzheimer disease compared with control subjects are highlighted (yellow indicates the most significant difference). Note relative sparing of occipital cortex.

Figure 4. Statistical parametric mapping analysis of typical vs atypical Alzheimer disease (AD). The patient with primary progressive aphasia (A) had retention of carbon 11-labeled Pittsburgh Compound B ($^{11}$C-PiB) predominantly in the left frontotemporal cortical region when compared with AD ($P < .01$). The patient with posterior cortical atrophy (B) had significantly higher $^{11}$C-PiB retention in the visual cortex than the subjects with typical AD ($P < .01$).
region located in proximity to the motor speech area (Broadmann area 44) and higher in the occipital cortex in the patient with PCA. Whether focal dementia syndromes are variants of AD is still controversial. Some authors believe the long disease course and early preservation of memory and insight make AD as the underlying pathological driving factor unlikely.6 Our 11C-PiB PET findings do support the concept of atypical AD at least in some cases of focal dementia. Although it is not possible to establish a cause-and-effect relationship with Aβ deposition in our 2 cases because we have no data on the time relationship between Aβ deposition and the onset of symptoms, the distinct 11C-PiB retention pattern and its concordance with clinical features and 18F-FDG hypometabolism suggests that Aβ may play a role in the pathogenesis.

Longitudinal studies with serial amyloid PET imaging and clinical assessment may provide insight into the role of Aβ in atypical dementia syndromes in a manner that postmortem studies cannot. Identification of Aβ may not only contribute to the differential diagnosis of dementia, but as anti-Aβ treatment options become available, it may also allow appropriate therapeutic strategies to be implemented and monitored, potentially preventing a focal deficit from becoming a global dementia.

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