Molecular Imaging With Pittsburgh Compound B Confirmed at Autopsy

A Case Report

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Objective: To determine the correspondence between uptake of Pittsburgh Compound B (PiB) in life and measures of β-amyloid (Aβ) in postmortem tissue analysis.

Patient: A 76-year-old man with a clinical diagnosis of dementia with Lewy bodies underwent fluorodeoxyglucose18F and PiB positron emission tomographic brain scans. Imaging revealed marked region specific binding of PiB and abnormal fluorodeoxyglucose uptake.

Intervention: Autopsy was performed 3 months after the PiB scan.

Results: Autopsy confirmed the clinical diagnosis; in addition, there was severe cerebral amyloid angiopathy and only moderate numbers of parenchymal Aβ plaques. Biochemical measures revealed a positive correlation between Aβ levels and regional PiB binding.

Conclusion: This report confirms that PiB detects Aβ in the living patient and demonstrates that amyloid deposited as cerebral amyloid angiopathy can be the dominant source of signal.

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and an autopsy was performed. A 60-minute dynamic brain PET acquisition with 15 mCi of 11C-PiB was performed and showed marked uptake in areas of the posterior cingulate, precuneus, and basal forebrain; rare tangles were seen in the entorhinal region as well as in cingulate and temporal cortices. Neuropathological findings characteristic of AD were also present with moderate numbers of neurofibrillary tangles in temporal and parietal cortices as well as in limbic regions, including the amygdala and basal forebrain; rare tangles were seen in the occipital cortex. The stage of AD based on the frequency and distribution of the tangles was Braak and Braak IV.2 There were several forms of Aβ pathology: severe bilateral cerebral amyloid angiopathy, moderate diffuse plaques, and rare cored plaques (Figure 2A). Diffuse plaques were frequent in the visual cortex but infrequent elsewhere; occasional cored plaques were seen in the parietal and occipital regions and were rare in other brain regions. Postmortem staining with 1µM of PiB and fluorescent detection revealed prominent PiB staining of cerebral amyloid angiopathy and dense cored plaques but not diffuse amyloid (Figure 2B). The overall frequency of plaques was low and met criteria from the Consortium to Establish a Registry for Alzheimer's Disease for "possible AD."6 Taking the tangles into consideration along with the plaques, the findings were consistent with an "intermediate likelihood of dementia due to AD," based on criteria from the National Institute on Aging–Reagan Institute,7 consistent with coexistent Lewy body disease. We measured soluble and insoluble Aβ40 and Aβ42 in frontal, parietal, and cingulate regions (Table) and compared these with measures of PiB binding in the homogenates and with measures of PiB binding obtained with PET (distribution volume ratios).8 Together, the biochemical and histological data demonstrate that positive PET imaging of PiB in life reflects the presence of amyloid pathology. The proportion of Aβ40 to total Aβ is greater than that expected in AD,9 supporting the strong contribution of vascular amyloid (Aβ40) to cortical amyloid load in this case.

**RESULTS**

The brain weighed 1420 g in the fresh state. There was no significant cortical atrophy evident. Moderate depigmentation of the substantia nigra and locus ceruleus was evident grossly. Microscopic examination confirmed the diagnosis of dementia with Lewy bodies, Braak stage IV.4 There were plentiful Lewy bodies in the substantia nigra with marked neuronal loss; there were Lewy bodies in the entorhinal region as well as in cingulate and temporal neocortices. Neuropathological findings characteristic of AD were also present with moderate numbers of neurofibrillary tangles in temporal and parietal cortices as well as in limbic regions, including the amygdala and basal forebrain; rare tangles were seen in the occipital cortex. The stage of AD based on the frequency and distribution of the tangles was Braak and Braak IV.2 There were several forms of Aβ pathology: severe bilateral cerebral amyloid angiopathy, moderate diffuse plaques, and rare cored plaques (Figure 2A). Diffuse plaques were frequent in the visual cortex but infrequent elsewhere; occasional cored plaques were seen in the parietal and occipital regions and were rare in other brain regions. Postmortem staining with 1µM of PiB and fluorescent detection revealed prominent PiB staining of cerebral amyloid angiopathy and dense cored plaques but not diffuse amyloid (Figure 2B). The overall frequency of plaques was low and met criteria from the Consortium to Establish a Registry for Alzheimer's Disease for "possible AD."6 Taking the tangles into consideration along with the plaques, the findings were consistent with an "intermediate likelihood of dementia due to AD," based on criteria from the National Institute on Aging–Reagan Institute,7 consistent with coexistent Lewy body disease. We measured soluble and insoluble Aβ40 and Aβ42 in frontal, parietal, and cingulate regions (Table) and compared these with measures of PiB binding in the homogenates and with measures of PiB binding obtained with PET (distribution volume ratios).8 Together, the biochemical and histological data demonstrate that positive PET imaging of PiB in life reflects the presence of amyloid pathology. The proportion of Aβ40 to total Aβ is greater than that expected in AD,9 supporting the strong contribution of vascular amyloid (Aβ40) to cortical amyloid load in this case.

**COMMENT**

To our knowledge, this study is the first pathological examination of a human brain from a patient who had a positive PiB scan during life. The autopsy confirmed the expectation that the PiB signal in life corresponds to Aβ deposits seen pathologically and measured biochemically after death. The brain contained relatively few mature cored plaques and had a restricted distribution of diffuse plaques that were present only in moderate numbers. Thus, based on criteria from the Consortium to Establish a Registry for Alzheimer’s Disease, the diagnosis of AD would be “possible” but not “probable” and certainly not “definite.” The most impressive finding was the severe cerebral amyloid angiopathy, which raises the notion that the PiB uptake in this case reflected Aβ in cerebral vessels more than Aβ in the brain parenchyma. Whether this observation is the rule or the exception must await additional clinical-pathological correlative
studies. It should be mentioned that PiB does not bind to Lewy bodies or neurofibrillary tangles at the tracer doses used for PET imaging, and even if it did, the scarcity of these intracellular pathologies would contribute negligible signal, especially compared with that from Aβ deposits.

Pittsburgh Compound B uptake appears sensitive to the presence of Aβ, but the specificity of a positive PiB scan is still under study. Uptake of PiB is a hallmark of AD and distinguishes most cases from normal controls. Subsequent research, however, indicates that up to 15% of apparently normal people have substantial cortical PiB binding. Brain amyloid accumulation is commonly seen in some elderly people at autopsy and whether these deposits are harbingers of dementia is under intense investigation. Most individuals with a diagnosis of mild cognitive impairment have positive PiB scans whereas some do not, and the proportion of PiB-positive subjects with mild cognitive impairment is similar to the proportion that ultimately develop AD. Our report substantiates the view that PiB uptake is a sensitive method to detect Aβ in the brain but points out the fact that clinical conditions other than probable or definite AD may harbor PiB-detectable amyloid deposits—thus broadening the range of clinically defined syndromes in which a PiB scan may be positive. Based on these findings, we would expect PiB retention to be a feature not only of AD, but also of (1) a normal elderly patient with amyloid deposition at risk for AD, (2) mild cognitive impairment, (3) cerebral amyloid angiopathy, and (4) dementia with Lewy bodies with amyloid pathology. It may be best not to equate amyloid deposition to clinical diagnosis from the outset but to think of PiB retention more fundamentally as a method to detect and quantify brain Aβ-amyloidosis.

As shown by the case in this report, it is also clear that several different dementia-associated pathologies (eg, Lewy bodies and threads, neurofibrillary tangles, infarcts, etc) can coexist even within a single brain. However, the clinical diagnosis, or even the pathological diagnosis based on consensus criteria, does not directly predict the presence or absence of Aβ deposition in these mixed states. The importance of amyloid imaging is as an objective measure of Aβ pathology. In many cases, this will be a diagnostic aid but will likely be of great value.

Studies comparing biochemical analysis of Aβ with quantitative PET in affected brain regions are provided in the Table below.

### Table. Comparison of Biochemical Analysis of Aβ With Quantitative PET in Affected Brain Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>DVR From PET Scan*</th>
<th>Soluble Aβ40 fmol/g</th>
<th>Soluble Aβ42 fmol/g</th>
<th>Insoluble Aβ40 pmol/g</th>
<th>Insoluble Aβ42 pmol/g</th>
<th>PiB Binding pmol/g†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>1.311</td>
<td>6938</td>
<td>14619</td>
<td>906</td>
<td>4685</td>
<td>444</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.299</td>
<td>6788</td>
<td>9554</td>
<td>882</td>
<td>3703</td>
<td>325</td>
</tr>
<tr>
<td>Cingulate</td>
<td>1.504</td>
<td>4342</td>
<td>9884</td>
<td>881</td>
<td>3884</td>
<td>556</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; DVR, distribution volume ratio; PET, positron emission tomography; PiB, Pittsburgh Compound B.

*Distribution volume ratio values were calculated from regions of interest within each brain region as described in Logan et al. Enzyme-linked immunosorbent assays were performed on homogenates of brain tissue from these regions using capture and detection antibodies from Takeda Pharmaceutical (Osaka, Japan) as previously described. Soluble fractions were extracted in Tris buffer, and insoluble fractions were extracted with formic acid. Parallel brain homogenates were analyzed with [H]PiB (1nM) for binding and normalized by wet tissue weight, as previously described.

†Binding of 1nM [H]PiB to tissue homogenates (picomole per gram wet weight). This does not represent saturating conditions.
in evaluating therapies aimed at reduction of Aβ pathology. In summary, this report describes a correspondence of amyloid pathology at autopsy with a positive PiB scan in life but demonstrates that amyloid deposited as cerebral amyloid angiopathy is the dominant source of signal.

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