Molecular Imaging With Pittsburgh Compound B Confirmed at Autopsy

A Case Report

Brian J. Bacskai, PhD; Matthew P. Frosch, MD, PhD; Stefanie H. Freeman, MD; Scott B. Raymond, BS; Jean C. Augustinack, PhD; Keith A. Johnson, MD; Michael C. Irizarry, MD; William E. Klunk, MD, PhD; Chester A. Mathis, PhD; Steven T. DeKosky, MD; Steven M. Greenberg, MD, PhD; Bradley T. Hyman, MD, PhD; John H. Growdon, MD

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.

Arch Neurol. 2007;64:431-434

Imaging brain amyloid during life with Pittsburgh Compound B (PiB) shows great promise as an aid to diagnosing Alzheimer disease (AD) and monitoring anti-β-amyloid (Aβ) therapies. Pittsburgh Compound B selectively binds to Aβ deposits in transgenic mice,1 crosses the blood-brain barrier, and results in a strong positron emission tomography (PET) signal in the cortex of human patients with AD.2 These observations are consistent with PiB’s detecting Aβ deposits in the living human brain, but this assumption has never been directly confirmed. One of the proposed criteria for establishing an AD biomarker was that the in vivo finding be verified at autopsy.3 We now report for the first time the neuropathological findings in the brain of a man with dementia whose PET scan revealed marked PiB uptake during life.

For editorial comment
see page 315

A 76-year-old man was evaluated for memory loss and gait disorder. Aside from a single unexplained fall roughly 4 years previously, he had been well until memory loss became apparent 2 years prior to evaluation. A neurologist diagnosed peripheral neuropathy and possible Parkinson disease and began treatment with pramipexol, which was subsequently discontinued because it was deemed ineffective. A fluorodeoxyglucose 18F PET scan performed 1 month prior to evaluation revealed reduced metabolism in both temporal and parietal cortices and mild reduction in the left frontal lobe; this pattern was consistent with AD. On examination, he reported having the fixed thought that a second (fictional) daughter was living in his house. He made 6 mistakes on the Information-Concentration-Memory subscore of the Blessed Dementia Scale, which ranges from 0 to 37 mistakes, 0 to 3 mistakes being within the normal range; the Mini-Mental State Examini-
and an autopsy was performed. A 76-year-old patient with dementia underwent a Positron emission tomography (PET) scan and Pittsburgh Compound B (PiB) scan. The PET images showed increased PiB uptake in the frontal and temporal cortices, with a distribution pattern consistent with Alzheimer's disease (AD). Two years later, the patient was re-evaluated and had developed motor symptoms but no significant change in cognitive function. The patient died, and a postmortem examination was performed.

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. 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. 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.” 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, 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). 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, 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 investigations.

**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. 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. 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.” 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, 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). 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, 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 investigations.

**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. 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. 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.” 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, 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). 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, supporting the strong contribution of vascular amyloid (Aβ40) to cortical amyloid load in this case.
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 in the future.
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 deposition as cerebral amyloid angiopathy is the dominant source of signal.

Accepted for Publication: October 19, 2006.

Correspondence: Brian J. Bacskai, PhD, Mass General Institute for Neurodegenerative Diseases, Department of Neurology, Massachusetts General Hospital, 114 16th St, Charlestown, MA 02129 (bbacskai@partners.org).

Author Contributions: Study concept and design: Bacskai, DeKosky, Hyman, and Growdon. Acquisition of data: Bacskai, Frosch, Freeman, Raymond, Augustinack, Johnson, Irizarry, Hyman, and Growdon. Analysis and interpretation of data: Bacskai, Frosch, Raymond, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. Drafting of the manuscript: Bacskai, Frosch, Freeman, Klunk, and Mathis. Critical revision of the manuscript for important intellectual content: Frosch, Raymond, Augustinack, Johnson, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. Statistical analysis: Irizarry. Obtained funding: Bacskai, Frosch, Freeman, Klunk, and Mathis. Critical revision of the manuscript for important intellectual content: Frosch, Raymond, Augustinack, Johnson, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. Statistical analysis: Irizarry. Obtained funding: Bacskai, Frosch, Freeman, Klunk, and Mathis. Critical revision of the manuscript for important intellectual content: Frosch, Raymond, Augustinack, Johnson, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. Financial Disclosure: G. E. Healthcare entered into a license agreement with the University of Pittsburgh based on the compound described in this article. Drs Klunk and Mathis are coinventors of Pittsburgh Compound B, and, as such, have a financial interest in this license agreement.

Funding/Support: This work was supported by grant EB00768 from the National Institutes of Health, grant AG 05134 from the Massachusetts Alzheimer’s Disease Research Center, and grant NS038372 from the Massachusetts General Hospital/Massachusetts Institute of Technology Udall Center of Excellence in Parkinson Disease Research.

REFERENCES