

Case Report/Case Series

Does a Positive Pittsburgh Compound B Scan in a Patient With Dementia Equal Alzheimer Disease?

Simon Ducharme, MD, MSc; Marie-Christine Guiot, MD, FRCPC;
James Nikelski, PhD; Howard Chertkow, MD, FRCPC

IMPORTANCE The clinical role of amyloid brain positron emission tomographic imaging in the diagnosis of Alzheimer disease is currently being formulated. The specificity of a positive amyloid scan is a matter of contention.

OBSERVATIONS An 83-year-old Canadian man presented with a 5-year history of predominantly short-term memory loss and functional impairment. Clinical evaluation revealed significant, gradually progressive short-term memory loss in the absence of any history of strokes or other neuropsychiatric symptoms. The patient met clinical criteria for probable Alzheimer disease but had a higher than expected burden of white matter disease on magnetic resonance imaging. A positron emission tomographic Pittsburgh Compound B scan was highly positive in typical Alzheimer disease distribution. The patient died of an intracerebral hemorrhage 6 months after the assessment. Autopsy revealed cerebral amyloid angiopathy in the complete absence of amyloid plaques or neurofibrillary tangles.

CONCLUSIONS AND RELEVANCE This patient demonstrates that a positive Pittsburgh Compound B scan in a patient with clinical dementia meeting criteria for probable Alzheimer disease is not proof of an Alzheimer disease pathophysiological process. A positive Pittsburgh Compound B scan in typical Alzheimer disease distribution in a patient with dementia can be secondary to cerebral amyloid angiopathy alone.

JAMA Neurol. 2013;70(7):912-914. doi:10.1001/jamaneurol.2013.420
Published online May 20, 2013.

Author Affiliations: Department of Neurology, Massachusetts General Hospital and McLean Hospital, Harvard University, Boston (Ducharme); Department of Psychiatry, McGill University, Montreal, Quebec, Canada (Ducharme); Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada (Guiot, Chertkow); Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, Quebec, Canada (Nikelski, Chertkow).

Corresponding Author: Howard Chertkow, MD, FRCPC, Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, 3755 Cote Ste-Catherine Rd, Montreal, QC H3T-1E2, Canada (howard.chertkow@mcgill.ca).

Carbon 11 (^{11}C)-labeled Pittsburgh Compound B (PiB) has been developed as a positron emission tomography (PET) ligand that binds to fibrillar β -amyloid.¹ The PiB PET scans are positive in 95% of patients with Alzheimer disease (AD) and about 60% of patients with mild cognitive impairment.^{2,3} Given the high specificity of PiB in cases of dementia as well as the US Food and Drug Administration's approval of similar amyloid PET imaging for clinical use (florbetapir F 18 injection [Amyvid]), this test is bound to be interpreted as an AD test despite reservations expressed by the scientific community and statements by the company that "a positive scan does not establish a diagnosis of Alzheimer's disease or other cognitive disorder."^{2,4} It is therefore crucial for clinicians to have a better sense of the sensitivity and specificity of this test. Herein, we report the first case, to our knowledge, of a patient with a clinical history suggestive of AD with a positive PiB scan who did not have any evidence of amyloid plaques or neurofibrillary tangles on autopsy.

Report of a Case

An 83-year-old man with a university-level education was assessed at the Memory Clinic of the Jewish General Hospital for

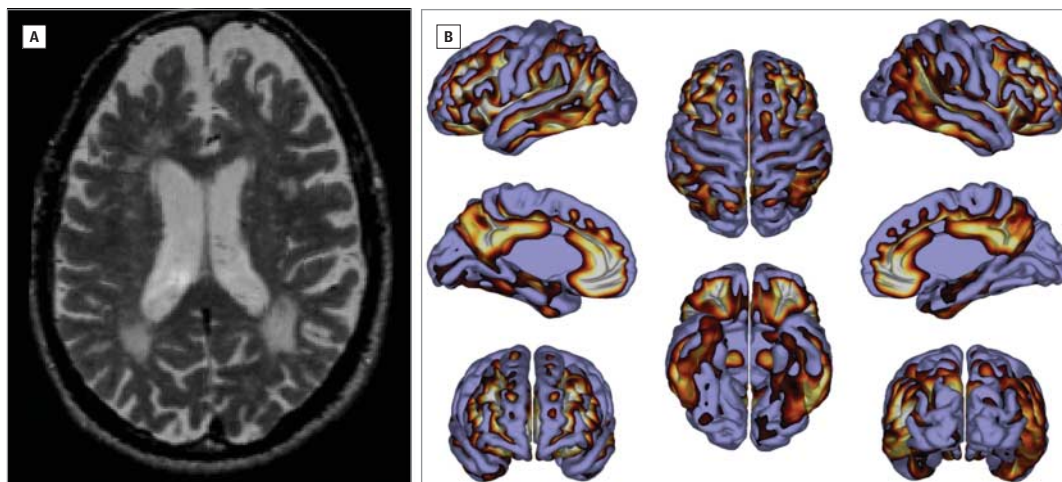
a 5-year history of memory loss. He was physically healthy with no history of strokes, hypertension, coronary artery disease, or psychiatric disorder. Familial history was negative for dementia.

Memory decline had begun insidiously at age 78 years, with gradual progression over time. Instrumental activities of daily living had been impaired since age 80 years. He had stopped driving and had become more withdrawn. There was no significant change in personality or other neuropsychiatric symptoms suggestive of Lewy body dementia or frontotemporal dementia.

Findings on physical examination including blood pressure and general neurological examination were entirely within normal limits. He had no primitive reflexes. There was no sign of parkinsonism. On cognitive examination, the Montreal Cognitive Assessment score was 17 of 30, including 0 of 5 on delayed recall.⁵ The Mini-Mental State Examination score was 23 of 30,⁶ with impairment in delayed verbal memory and orientation but relatively preserved attention and language. There were impairments in executive function, clock drawing, and calculation. A complete neuropsychological evaluation completed in February 2010 confirmed this profile.

The dementia biochemical workup findings were normal except for mild hyperglycemia (fasting glucose, 127.9 mg/dL;

Figure 1. Magnetic Resonance Image and Positron Emission Tomographic Scan



A, Axial T2-weighted magnetic resonance imaging showing prominent periventricular white matter changes. B, Positive carbon 11-labeled Pittsburgh Compound B positron emission tomographic scan showing β -amyloid (light

color) in typical Alzheimer disease distribution, superimposed on a 3-dimensional rendering of the patient's structural magnetic resonance image (dark color).

to convert to millimoles per liter, multiply by 0.0555). A computed tomographic scan showed moderate diffuse atrophy with periventricular white matter hypodensities. Given the clinical presentation and limited vascular risk factors, the patient was diagnosed as meeting criteria for probable AD⁷ in addition to type 2 diabetes mellitus. Treatment was begun with the cholinesterase inhibitor donepezil hydrochloride, 10 mg/d, with little obvious change in cognition at follow-up.

The patient consented to involvement in research studies of natural history, including neuroimaging. A T1-weighted magnetic resonance image and a T2-weighted fast spin-echo magnetic resonance image were acquired on a 1.5-T scanner using magnetization-prepared rapid acquisition with gradient-echo pulse sequences with 1.2-mm-thick sagittal slices. This demonstrated prominent confluent white matter changes (Figure 1). There was no clear evidence of infarction or microbleeds, although gradient-echo sequence was not carried out. Imaging with PET using [¹¹C]PiB was carried out at the Montreal Neurological Institute using 15-mCi injection over 20 seconds, a waiting period of 50 minutes, and then image acquisition over 40 minutes. The PET data were acquired on a Siemens/CTI ECAT HR+ scanner in 3-dimensional imaging mode (63 parallel planes). The standardized uptake value ratio was determined by normalizing tissue radioactivity concentration for each of 48 brain regions against radioactivity in cerebellar gray matter. The PiB visual rating was strongly positive, with ligand distribution in a pattern typical for AD. The standardized uptake value ratio was also positive at 1.83 (our cutoff for a positive scan is a standardized uptake value ratio of 1.24), with a large amyloid distribution typical for AD (Figure 1). In the new lexicon, the positive amyloid imaging (but unusual magnetic resonance imaging results) was taken to give intermediate biomarker support to the clinical diagnosis of probable AD.³

Six months later, the patient presented with sudden collapse and left hemiparesis. A repeated cerebral computed tomographic

scan showed massive right intracerebral hemorrhage compatible with amyloid angiopathy. The patient died 4 hours later.

At autopsy, there was a right intracerebral hemorrhage extending from the right superotemporal region to the midline and breaking into the ventricular system at the level of the amygdala. There were numerous recent hemorrhages in the midbrain and pons. No old cerebral infarctions were noted. Microscopic examination showed no senile plaques or neurofibrillary tangles in any part of the brain and no microscopic evidence even suggestive of AD. Indeed, the prominent microscopic finding was of a diffuse cerebral amyloid angiopathy (CAA) affecting all the lobes with a predilection for the occipital lobe (Figure 2). The striking absence of amyloid plaques and neurofibrillary tangles, hallmarks of AD-type histological changes, excluded the diagnosis of AD. Therefore, the final pathological diagnosis was vascular dementia secondary to CAA.

Discussion

Cerebral amyloid angiopathy is characterized by deposition of amyloid in the media and adventitia of small and medium-sized blood vessels of the cerebral cortex and leptomeninges.⁸ It is frequently asymptomatic, but it constitutes an important cause of primary intracerebral hemorrhage in elderly individuals.⁸ Incidence increases with age, and some degree of CAA has been found in up to 36% of brains of autopsied individuals older than 60 years.⁹ This is about twice the number of individuals with clinical AD dementia or "prodromal AD." Amyloid deposits seen in the sporadic form of CAA are similar to the material found in senile plaques of AD. About 25% of subjects with AD have moderate to severe CAA on autopsy, but fewer than 50% of patients with CAA meet pathological criteria for AD.^{8,10}

According to the recent National Institute on Aging-Alzheimer's Association diagnostic criteria, this patient would

Figure 2. Postmortem Immunohistochemistry for β -Amyloid in the Occipital Lobe



Absence of positive amyloid plaques and presence of numerous intraparenchymal cortical and subarachnoid vessels demonstrated strong positivity for β -amyloid (clone 6F/3D [Dako Corp], original magnification $\times 20$).

have been classified prior to his hemorrhagic stroke as having probable AD dementia by clinical criteria, with intermediate probability of the AD pathophysiological process (evidence of β -amyloid on imaging without available evidence of neuronal injury).³ The autopsy revealed that both clinical criteria and PiB imaging wrongly supported a diagnosis of AD. The only clinical cue to the correct diagnosis of vascular dementia was the presence of confluent white matter changes on magnetic resonance imaging.

It has been demonstrated that PiB binds to amyloid in vessel walls.^{11,12} Binding of PiB is increased in individuals with CAA compared with controls, but less so than in subjects with AD.^{12,13} The occipital to global uptake ratio tends to be more pronounced in CAA, paralleling the preferential posterior distribution of cerebral hemorrhages.^{12,13} There is one published report of a patient with Lewy body dementia with a positive PiB scan due to CAA, but the concurrent pathological evidence of amyloid plaques and neurofibrillary tangles complicated this case.¹¹ To our knowledge, we are the first to describe a positive PiB scan in typical AD distribution in a patient with dementia in the complete absence of significant amyloid plaques and neurofibrillary tangles.

As AD biomarkers become more accessible and even routinized in dementia and mild cognitive impairment, we must recognize that a positive PiB scan is not synonymous with AD in patients with dementia and that positive PiB results suggestive of AD can be present in CAA, which is a common brain pathology.⁹ Indeed, recent US Food and Drug Administration regulatory guidelines for Amyvid stress that while a negative scan is useful to exclude the diagnosis of AD, a positive scan is not a definitive test for AD. The presence of prominent white matter changes on magnetic resonance imaging in the absence of vascular risk factors should raise the possibility of a CAA diagnosis.¹⁴ Because CAA is often asymptomatic in elderly individuals, we would also speculate that a certain percentage of cognitively normal individuals who have positive amyloid PET imaging¹⁵ in fact could have CAA rather than AD.¹⁶

ARTICLE INFORMATION

Accepted for Publication: February 14, 2013.

Published Online: May 20, 2013.
doi:10.1001/jamaneuro.2013.420.

Author Contributions: *Study concept and design:* Ducharme and Chertkow.

Acquisition of data: Guiot and Chertkow.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Ducharme, Guiot, and Chertkow.

Critical revision of the manuscript for important intellectual content: Guiot, Nikelski, and Chertkow.

Statistical analysis: Nikelski.

Obtained funding: Chertkow.

Administrative, technical, and material support: Guiot.

Study supervision: Chertkow.

Conflict of Interest Disclosures: Dr Chertkow sits on an adjudication board for clinical trials for Bristol-Myers Squibb and has been a speaker and advisory board member for Pfizer Canada.

Funding/Support: Dr Chertkow is supported by operating grants from the Canadian Institutes for Health Research and the Fonds de la recherche en santé du Québec.

REFERENCES

1. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55(3):306-319.

2. Rowe CC, Ng S, Ackermann U, et al. Imaging β -amyloid burden in aging and dementia. *Neurology*. 2007;68(20):1718-1725.

3. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.

4. Rabinovici GD, Furst AJ, O'Neil JP, et al. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*. 2007;68(15):1205-1212.

5. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.

6. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

7. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.

8. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol*. 2011;70(6):871-880.

9. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: incidence and complications in the

aging brain, II: the distribution of amyloid vascular changes. *Stroke*. 1983;14(6):924-928.

10. Ellis RJ, Olichney JM, Thal LJ, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, part XV. *Neurology*. 1996;46(6):1592-1596.

11. Bacskai BJ, Frosch MP, Freeman SH, et al. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. *Arch Neurol*. 2007;64(3):431-434.

12. Johnson KA, Gregas M, Becker JA, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Ann Neurol*. 2007;62(3):229-234.

13. Ly JV, Donnan GA, Villemagne VL, et al. 11C-PIB binding is increased in patients with cerebral amyloid angiopathy-related hemorrhage. *Neurology*. 2010;74(6):487-493.

14. Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. *Stroke*. 2004;35(11)(suppl 1):2616-2619.

15. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292.

16. Gurol ME, Dierksen G, Betensky R, et al. Predicting sites of new hemorrhage with amyloid imaging in cerebral amyloid angiopathy. *Neurology*. 2012;79(4):320-326.