Usefulness of positron emission tomography to detect cerebral amyloid as a means to diagnose neurodegenerative disease

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Alzheimer's disease is characterized histologically by the accumulation of a subtype of amyloid protein—beta amyloid—in the brain parenchyma in the form of amyloid plaques. In another neurodegenerative disorder, cerebral amyloid angiopathy, the accumulation of beta amyloid occurs within the walls of the cerebral vessels. With recent advances in imaging technology, we can not only image amyloid plaques in the brain parenchyma at an earlier stage of disease, but can also often correlate the presence of Alzheimer's disease with cerebral amyloid angiopathy. We present a case of suspected Alzheimer's disease and discuss the association in this patient between cerebral amyloid angiopathy and Alzheimer's disease, as well as the benefits of a unique nuclear imaging modality, amyloid positron emission tomography, in diagnosing dementia.

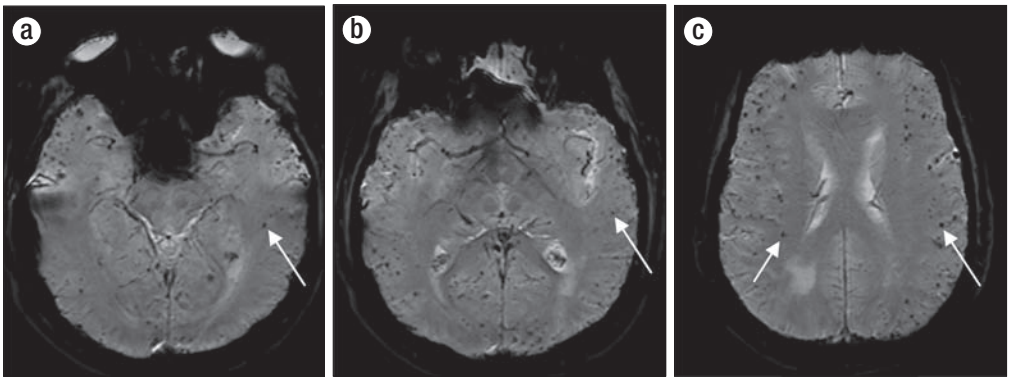

Figure 1. Several susceptibility-weighted MR images through the brain depict the widespread foci of hemosiderin staining (arrows) from chronic microhemorrhages, characteristic of cerebral amyloid angiopathy.

Dementia is characterized by a progressive deterioration in multiple neurological functions, including memory, thinking, behavior, and ability to perform daily tasks. The number of people living with dementia was estimated at 47.5 million in 2015 and is expected to reach 75.6 million by 2030 (1). Currently, the cost burden related to dementia is estimated at US $604 billion, and this will likely increase exponentially over the next few decades (1). If experimental therapies to remove or reduce the production of amyloid in the brain can be shown to be effective, early detection of Alzheimer's disease (AD) and other dementias could be important in terms of slowing progression of the disease. In recent years, a nuclear imaging technique has been developed that utilizes one of several similar radiotracers, including Amyvid (Florbetapir F-18), to selectively highlight and image amyloid plaques, which are abundant in the brains of patients with AD.

CASE REPORT

A 68-year-old man presented for progressive memory loss over the past 2 years. A detailed neuropsychological evaluation found him to have an intermediate probability of having AD. Brain magnetic resonance imaging (MRI) disclosed many punctate foci of signal dropout in a widespread distribution on susceptibility-weighted images *(Figure 1),* correlating with the presence of many chronic microhemorrhages.

The patient also participated in the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study, which examines how brain imaging, specifically amyloid positron emission tomography (PET) scan, can assist clinicians in diagnosing and treating AD and other dementias. As opposed to a normal amyloid scan *(Figure 2a, 2b),* the patient's scan demonstrated a widespread abnormal increase in radiotracer accumulation within the cortical gray matter resulting in loss of gray-white matter distinction *(Figure 2c, 2d).*

DISCUSSION

Until recently, imaging had a limited role in the diagnosis of dementia. The primary means of diagnosing AD is currently neuropsychological evaluation utilizing a set of clinical criteria, a method that is neither sensitive nor specific. Recent advances,

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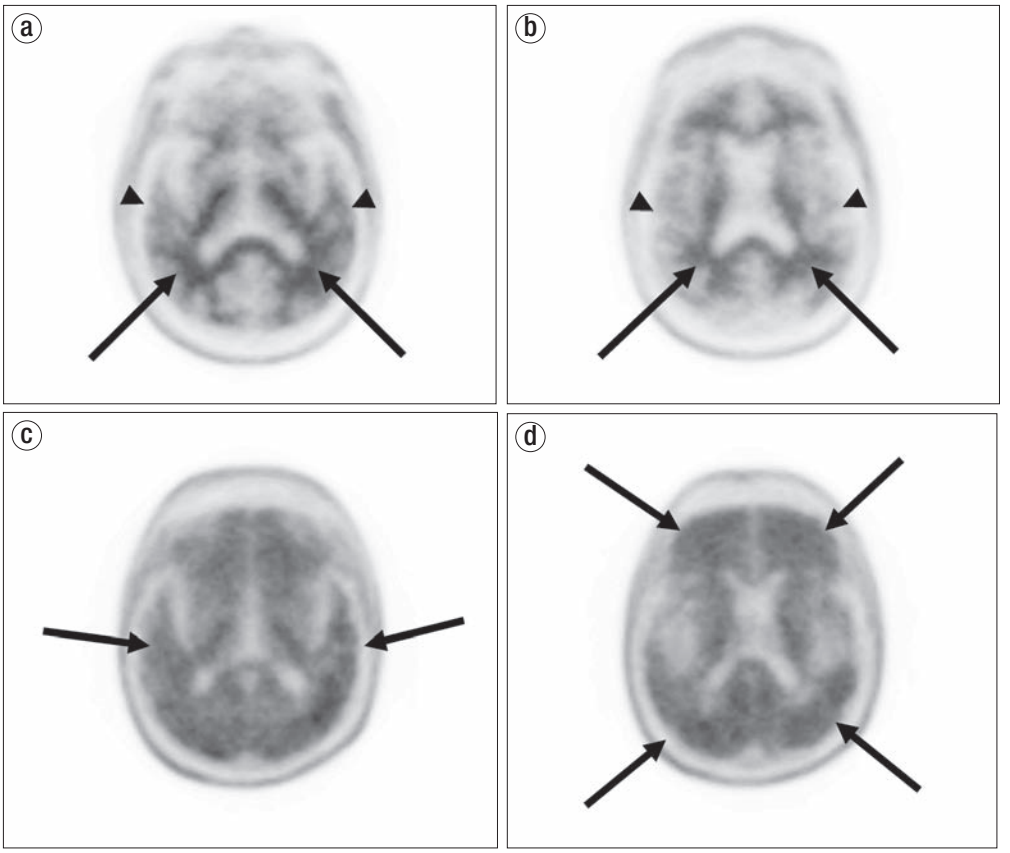

Figure 2. Normal Amyvid scan at the level of **(a)** the Sylvian fissures and **(b)** the lateral ventricles. Note the greater accumulation of the radiotracer within the white matter (arrows) as opposed to the cortical gray matter (arrowheads), resulting in clear gray-white matter distinction. Abnormal Amyvid scan at the level of **(c)** the Sylvian fissures and **(d)** the lateral ventricles. Note the increase in radiotracer accumulation throughout the gray matter resulting in diffuse loss of gray-white matter distinction (arrows). Amyvid tracer localizes specifically to amyloid plaques. This positive scan indicates the presence of an extensive plaque burden.

however, have made neuroimaging, including brain MRI and PET, a useful adjunct in differentiating dementia from normal sequelae of aging.

MRI, specifically susceptibility-weighted sequences, aid significantly in the detection of cerebral amyloid angiopathy (CAA), a cerebrovascular disorder characterized by accumulation of cerebral beta amyloid protein (Aβ) in the tunica media and adventitia of leptomeningeal and cortical vessels. One manifestation of this disorder is the accumulation over time of many small, often clinically silent microhemorrhages, as was demonstrated in our patient. Other presentations include acute lobar hemorrhage, small-vessel infarcts, and leukoencephalopathy (2).

CAA is a degenerative disease found primarily in the elderly, and while evidence of CAA is found incidentally at autopsy in 30% of asymptomatic elderly individuals, it is found at a much higher rate (90%–96%) in autopsies of patients with AD (3). Studies have shown that AD results from abnormal deposition of the same amyloid protein subtype—Aβ—as seen in CAA (3). Whereas in CAA the deposition of Aβ is within the vasculature, in AD it is within the brain parenchyma itself (4). This results in the formation of amyloid plaques in the brain. While these plaques can be found normally in the aging brain, they are found in far greater number and with a more widespread distribution in the AD brain.

Evidence now predominantly points to the failure of perivascular lymphatic drainage of Aβ as a major common factor in the pathogenesis of both CAA and AD. Elimination of Aβ is a multistep pathway involving enzymatic degradation of the parent protein, absorption of the components into the blood, and drainage of the components along perivascular lymphatic channels. Each of these individual elimination mechanisms appears to fail as the aging brain experiences reduction of enzymatic activity and stiffening of cerebral arteries, resulting in decreased absorption into the blood and impaired drainage. This in turn results in accumulation of Aβ in the brain (3).

While amyloid plaques could previously be visualized only at autopsy, a new imaging technique, amyloid PET scan, allows for the direct visualization of the overall burden and distribution pattern of amyloid plaques via the high-affinity binding of Amyvid (Florbetapir F-18) or other similar radioisotopes to amyloid plaques in the brain. A positive amyloid scan, as seen in our patient, is indicative of moderate to frequent amyloid plaques. Of note, there is no similar biomarker for CAA, and based on imaging it is possible that our patient has both disorders. Since a degree of amyloid plaque accumulation can also be seen in elderly patients without AD, amyloid imaging should be used as an adjunct to clinical diagnostic evaluation. A negative amyloid scan indicates sparse to no amyloid plaques and is inconsistent with a diagnosis of AD (5). A negative amyloid scan in a patient who has a clinical diagnosis of AD has been shown to be of great clinical value, as it suggests a misdiagnosis and often results in changes to subsequent therapeutic planning (6).

Currently, there is a lack of efficacious drugs targeted for removing or reducing production of amyloid. However, several new targeted drugs for AD therapy are being researched and, should a drug prove effective, it is reasonable that diagnosis of AD at the earliest possible stage would be advantageous in terms of initiating treatment and slowing progression of the disease. Amyloid PET imaging, particularly as part of a multimodality neuroimaging approach in combination with MRI, is a valuable adjunct to standard neuropsychological testing in this context.

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