Letters to the Editor

Alzheimer Disease: Approaches to Early Diagnosis and High-Accuracy Imaging

TO THE EDITOR: The development and application of ligands for PET imaging of Alzheimer disease (AD) has evolved into an important tool for the clinical diagnosis of AD. Among the promising ligands, Pittsburgh compound B (PiB), developed by Mathis et al. (*1*) and Klunk et al. (*2*), is one well-known example. In cooperation with Långström and his group in Uppsala, PiB was labeled with ^{11}C and applied clinically (*3*). The tracer was soon used in many other academic centers and initiated such continuous interest that 3 compounds—[18]F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben—obtained approval by the Food and Drug Administration for regular clinical application.

Kobylecki et al. evaluated ^{18}F-florbetapir in patients with AD and frontotemporal dementia and in healthy controls (*4*). When PET images were masked to clinical data and regional analysis, trained interpreters had positive results in 80% of AD patients but also in 25% of patients with frontotemporal dementia and 10% of healthy controls. If all clinical information and sources of error, such as atrophy, increased white matter accumulation, or movement during registration, were taken into consideration, the interpreters could discriminate frontotemporal dementia and AD. In his perspective, Frey discussed the results in a comprehensive and conclusive way (*5*). In any case, increased training of interpreters remains highly advisable, but alternatively, PET imaging of Aβ plaques may be improved by a variation of protocols. Therefore, I am writing this letter to draw attention to two promising approaches to both early diagnosis of AD and highly accurate PET assays.

The approach to early diagnosis of AD is to extend PET imaging to tracer binding in plaques within muscles. PET imaging of such plaques was successfully demonstrated by Maetzler et al. with ^{11}C-PiB (*6*). In general, the existence of plaques in muscles is known as inclusion body myositis (IBM), and the PET findings indicated amyloid β deposition. Recently, in a comprehensive experimental study, Schuh et al. showed that amyloid plaque formation follows the same mechanism in muscle as in brain (*7*). Moreover, amyloid precursor proteins were found as observed in the brain. The work of Schuh et al. brings up an interesting approach to the early diagnosis of AD or at least widens the window for follow-up studies during disease progression.

The approach to highly accurate PET assays is pharmacokinetic analysis of PET data, because the metabolic assessment is performed in a precisely defined way. If the data are analyzed by a 3-compartment model (also known as the 2-tissue-compartment model), the rates of plaque binding (k_3) and release (k_4) can be calculated. Independently of binding rates, tracer delivery from the blood is determined by K_1. In AD, blood flow is known to decrease with disease progression. Therefore, increased tracer binding to plaques may be obscured by decreased tracer delivery to the region of interest. Even if reference regions are used, these regions are not ensured to be good controls.

In any case, during disease progression, alterations in blood flow and metabolism must be assumed to proceed differently from and independently of each other. In a longitudinal study with 2 mouse models, Maier et al. impressively showed blood flow to decrease drastically in late phases of the disease (*8*). Tracer binding, however, remained at a plateau, indicating a stable disease phase. Alternatively, pharmacokinetic analysis may show increased tracer release (k_4), which compensates for higher uptake rates (k_3). Pharmacokinetic analysis directly reveals the metabolic pathways ongoing with AD and allows consequent discrimination of the various velocity constants. In any case, the prerequisite is dynamic PET registration, for which all PET systems are sensitive and fast enough. Using appropriate subroutines, pharmacokinetic calculations can be performed to create parametric images.

Pharmacokinetic modeling is well proven in PET imaging but is not the focus of the community and, at least, is not thought to be suited to routine PET applications. Shen et al. (*9*) and Palner et al. (*10*) recently presented a striking illustration of the possible key role of pharmacokinetic calculations. In the case of apoptosis resulting from chemotherapy, they obtained PET results that were highly significant but values that remained small, below 3% injected dose per gram. However, pharmacokinetic analysis revealed uptake rates (k_3) that were 3-fold higher in apoptotic cells. Thus, the way to clinical translation is well paved.

In plaque imaging, sources of error include movement during PET registration, atrophy, and increased accumulation in white matter. Therefore, simultaneous registration by PET/MR imaging has already been proven particularly advantageous and opens a way to direct translation to clinical applications, as discussed by Wehrl et al. (*11,12*).

In summary, the extension of PET imaging to amyloid plaques in muscles to gain a broader view of AD progression, perhaps including early disease phases, seems promising. In addition, pharmacokinetic analysis of PET data may allow us to determine metabolic parameters that play a key role, particularly in follow-up studies of AD.

REFERENCES

1. Mathis CA, Bacskai BJ, Kajdasz ST, et al. A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain. *Bioorg Med Chem Lett.* 2002;12:295–298.
2. Klunk WE, Wang Y, Huang GF, et al. The binding of 2-(49-methylaminophenyl) benzothiazole to postmortem brain homogenates is dominated by the amyloid component. *J Neurosci.* 2003;23:2086–2092.
3. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol.* 2004;55:306–319.
4. Kobylecki C, Langheinrich T, Hinz R, et al. F-florbetapir positron emission tomography in patients with frontotemporal dementia and Alzheimer's disease. *J Nucl Med.* 2015;56:386–391.
5. Frey KA. Amyloid imaging in dementia: contribution or confusion? *J Nucl Med.* 2015;56:331–332.
6. Maetzler W, Reimold M, Schittenhelm J, et al. Increased [11C]PIB-PET levels in inclusion body myositis are indicative of amyloid β deposition [letter]. *J Neurol Neurosurg Psychiatry.* 2011;82:1060–1062.
7. Schuh RA, Jackson KC, Schlappal AE, et al. Mitochondrial oxygen consumption deficits in skeletal muscle isolated from an Alzheimer's disease-relevant murine model. *BMC Neurosci.* 2014;15:24.
8. Maier FC, Wehrl HF, Schmid AM, et al. Longitudinal PET-MRI reveals β-amyloid deposition and rCBF dynamics and connects vascular amyloidosis to quantitative loss of perfusion. *Nat Med.* 2014;20:1485–1492.

9. Shen B, Jeon J, Palner M, et al. Positron emission tomography imaging of drug-induced tumor apoptosis with a caspase-triggered nanoaggregation probe. *Angew Chem Int Ed Engl.* 2013;52:10511–10514.
10. Palner M, Shen B, Jeon J, et al. Preclinical kinetic analysis of the caspase-3/7 PET tracer ^{18}F-C-SNAT for imaging tumor apoptosis after chemotherapeutic treatment. *J Nucl Med.* June 4, 2015 [Epub ahead of print].
11. Wehrl HF, Wiehr S, Divine MR, et al. Preclinical and translational PET/MR imaging. *J Nucl Med.* 2014;55(suppl):11S–18S.
12. Wehrl HF, Sauter AW, Divine MR, et al. Combined PET/MR: a technology becomes mature. *J Nucl Med.* 2015;56:165–168.

Hans-Jürgen Machulla
Eberhard Karls University of Tuebingen
Ziegelhuettestrasse 46 Tuebingen D-72072, Germany
E-mail: machulla@uni-tuebingen.de

REPLY: Dr. Machulla suggests modifications of tracer imaging approaches to the clinical investigation of Aβ-amyloid deposition in dementia. He suggests the potential value of two embellishments on the current clinical practice guidelines for brain amyloid imaging: imaging of skeletal muscle in addition to the brain and use of dynamic data collection with tracer kinetic analyses.

Regarding the proposed addition of skeletal muscle imaging to detect early changes in Aβ-amyloid deposition in dementia, the present understanding of pathologic amyloidosis is not encouraging. Dr. Machulla points out that Aβ deposits in skeletal muscle in inclusion body myositis (IBM) are labeled with ^{11}C-Pittsburgh compound B (^{11}C-PiB) as support for potential extension to suspected cases of Alzheimer disease (AD). Myopathy in IBM is known to include deposition of Aβ-amyloid (*1*); hence, finding increased ^{11}C-PiB binding is not unexpected. However, myopathy (including IBM) is not characteristic of AD or other neurodegenerative dementias, even in advanced stages. Imaging of skeletal muscle to advance the diagnosis of AD is therefore not supported by the available pathologic evidence. In terms of early AD diagnosis, evidence accumulating from many laboratories indicates that Aβ-amyloid biomarkers (both PET tracer binding and cerebrospinal fluid alterations) are abnormal for years, if not decades, before dementia diagnosis (*2*). The addition of muscle imaging to PET brain Aβ-amyloid imaging sessions is unlikely to produce meaningful insight.

I agree with Dr. Machulla that application of compartmental tracer kinetic analysis has potential to improve the specificity of imaging. As he correctly points out, however, this approach may be difficult to accomplish on a routine clinical basis, because careful attention to subject cooperation with longer scanning sessions and more complex data reconstructions and image analyses are required. There are previously reported data demonstrating significant differences between standardized uptake value ratios and kinetically determined binding measures in AD subjects studied with ^{11}C-PiB (*3*). These differences are significant in comparison to rates of change over a few years but are not as clearly important in the distinction of amyloid-positive versus -negative cross-sectional classifications.

Further development and work are needed and underway to establish automated analyses of amyloid ligand distributions that may ultimately assist clinical classification of individual subjects. Until one or more of these approaches are validated and adopted, molecular imaging experts must exercise caution in interpreting results and must be aware of the potential confounding effects of subject motion and cerebrocortical atrophy in the clinical reporting of amyloid images.

REFERENCES

1. Nogalska A, D'Agostino C, Engel WK, Askanas V. Activation of the gamma-secretase complex and presence of gamma-secretase-activating protein may contribute to Aβ42 production in sporadic inclusion-body myositis muscle fibers. *Neurobiol Dis.* 2012;48:141–149.
2. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia. *JAMA.* 2015;313:1924–1938.
3. van Berckel BN, Ossenkoppele R, Tolboom N, et al. Longitudinal amyloid imaging using ^{11}C-PiB: methodologic considerations. *J Nucl Med.* 2013;54:1570–1576.

Kirk A. Frey
University of Michigan Hospitals
Room B1 G505 UH 1500
East Medical Center Dr.
Ann Arbor, MI 48109-0028
E-mail: kfrey@umich.edu