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PET: Differentiating Neurodegenerative Disorders

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With the increasing age of the U.S. population, healthcare professionals expect to see a concurrent and significant rise in the number of people afflicted with some form of neurodementia, including Alzheimer's disease.

"It has a lot to do with physical survival. People are living longer and, as a result, the number of dementia cases are, and will be, increasing," says Alan D. Waxman, MD, chief of nuclear medicine and cochair of the imaging center at Cedars-Sinai Medical Center in Los Angeles.

The current statistics are already grim. According to the Alzheimer's Association's 2007 Facts and Figures, an estimated 5.1 million people in the United States have Alzheimer's disease, with nearly 5 million of them over age 65. The remainder is under the age of 65 and considered "early onset" cases. Every 72 seconds, someone develops Alzheimer's disease, which is the most common form of dementia. This accounts for 50% to 70% of such cases, which are expected to triple by 2050.

As such, early diagnosis will be critical toward improving treatment, not only for Alzheimer's disease but for all dementias. Advancements in PET imaging—including fluorodeoxyglucose (FDG)-PET, as well as synthesized molecules such as fluorine-18 dimethylamino-dicyano-naphthalene propene (FDDNP)—may help physicians achieve that important early diagnosis and also distinguish between different forms of dementia. Two recent studies point in this direction.

Differentiating Disease via FDG

As demonstrated in a recent study, FDG-PET, which involves the injection of a short-life radioactive form of sugar (FDG) during PET scans, can significantly improve accuracy in diagnosing frontotemporal dementia (FTD), which is often mistaken for Alzheimer's disease.

FTD, a common cause of early dementia, typically afflicts people ranging from the ages of 45 to 64 and is characterized by behavioral changes and language difficulties. Because its symptoms often match the clinical diagnostic criteria for Alzheimer's, it is often misdiagnosed.

"Both FTD and Alzheimer's disease are gradual, progressive neurodegenerative diseases," explains Norman L. Foster, MD, professor of neurology and director of the Center for Alzheimer's Care, Imaging, and Research at the University of Utah School of Medicine. "With Alzheimer's disease, memory loss is the first and foremost symptom. There are no physical findings, such as reflex changes or other biomarkers, to help physicians recognize the condition. Similarly, FTD has no obvious findings on the physical examination. The first and most prominent symptoms are behavioral changes and, sometimes, language difficulties."

These factors pose a conundrum for physicians, Foster explains. Memory loss seen in Alzheimer's disease also occurs in FTD. At the same time, behavioral changes and language difficulties also occur in Alzheimer's. "Currently, the physician has to make a judgment whether the predominant symptom is memory loss or behavioral change and language difficulties," he says. "This can be difficult, especially if patient history is unreliable or unavailable. Using clinical methods alone, physicians have a difficult time distinguishing between the two."

As a result, patients may undergo hospitalization and treatment, including drug administration, for the wrong disease. But a correct diagnosis can eliminate costs and side effects related to unnecessary treatment, according to Foster.

Typically, one third of FTD patients have a family history of a similar dementia disorder. Thus, by combining available patient medical history, psychometric testing, and FDG-PET, physicians can better differentiate between FTD and early Alzheimer's disease. That's the conclusion of a recent study led by Foster and reported in the October issue of *Brain*.

"Our study asked a very specific question: 'Could FDG-PET improve accuracy and confidence in a correct diagnosis?'" says Foster. The answer appears to be yes. The research demonstrated that FDG-PET offers a convincing and reliable test to help physicians make that important distinction between FTD and Alzheimer's disease, as well as an effective tool in the early treatment of FTD.

Still, PET scans alone can't confirm the distinction between FTD and Alzheimer's disease. Medical history and examination remain crucial components to dementia evaluation. But FDG-PET shows different patterns of hypometabolism in these disorders that help provide the differential diagnosis. "We looked at hypometabolism patterns, which is much more challenging than just finding a hot or cold spot [and] is the focus of many nuclear medicine scans," says Foster.

Postmortem Assessment

In the study, which was funded by the National Institute on Aging (NIA), six researchers from three national Alzheimer's disease centers accurately distinguished between FTD and Alzheimer's in nearly 90% of cases, representing a nearly 14% improvement over standard clinical diagnostic methods.

Researchers examined medical records and FDG-PET scans of 45 deceased patients and their autopsies. Microscopic examination revealed that 31 had Alzheimer's and 14 had FTD. "We were presented with a great opportunity because the subjects had received PET scans as part of an evaluation at an Alzheimer's center," says Foster. "When they died, they had microscopic brain examinations."

Using clinical information and FDG-PET images, neurologists with a range of experience were then asked to determine what had caused each patient's dementia. Specifically, the neurologists used the following five methods:

- review of clinical summaries;
- a diagnostic checklist;
- summary and checklist;
- transaxial FDG-PET scans; and
- FDG-PET stereotactic surface projection (SSP) metabolic and statistical maps—SSP summarizes brain activity changes and, through statistical analysis, reveals significant areas of damage.

When using only clinical methods, the neurologists accurately distinguished between FTD and Alzheimer's in 76% to 79% of the cases. When using only FDG-PET scans, they were able to accurately distinguish FTD from Alzheimer's in 85% to 89% of cases. Combined FDG-PET and clinical information increased diagnostic accuracy from 79% to 90%. Further, researchers achieved highest diagnostic accuracy (89.6%) with SSP displays, as well as highest specificity (97.6%) and sensitivity (86%) and positive likelihood ratio for FTD (36.5).

Researchers concluded that FDG-PET visual interpretation following training was more reliable and accurate in distinguishing FTD from Alzheimer's disease than with only clinical methods. Moreover, the researchers indicated that FDG-PET provides added information, increasing diagnostic confidence even among experienced dementia specialists.

At the Molecular Level

Another recent area of research involves imaging the presence of beta amyloids in the brains of patients with Alzheimer's disease, which has been accomplished through a combination of PET imaging and molecular amyloid targeting agents such as FDDNP.

"More and more investigators are demonstrating a great deal of interest in looking directly for Alzheimer's disease through beta amyloid detection," says Waxman. "New molecules are being developed to detect beta amyloids as the level of beta amyloids may correlate with the potential for developing Alzheimer's disease, even in early cases. So a variety of things are being done that will allow us to more clearly define if a person is a candidate for Alzheimer's disease or some other form of neurodementia."

Recently, California researchers demonstrated how FDDNP, a relatively new compound, can be applied to brain imaging to provide an effective method for diagnosing patients with Alzheimer's. Their study, which was published in the December 21, 2006, issue of *The New England Journal of Medicine* ("PET of Brain Amyloid and Tau in Mild Cognitive Impairment"), not only illustrated the viability of this method but indicated that FDDNP could be useful in evaluating new therapies to treat or prevent Alzheimer's disease.

FDDNP reveals the deleterious physical impact that Alzheimer's disease has on the brain, as it can help find the abnormal proteins that form what are called amyloid senile plaques and tau neurofibrillary tangles found in patients' brains. Specifically, these deposits are found in the cortical region, and FDDNP reveals their presence by binding to them.

"We found that when we inject FDDNP into a patient or research subject, the area of the brain that collects the deposits has higher binding values in areas that don't have those deposits," says the study's lead author Gary Small, MD, professor of psychiatry and biobehavioral sciences and director of the UCLA Center on Aging.

Previously, the most successful method for finding these deposits in vivo was through surgical removal of brain tissue. But PET scanning combined with FDDNP offers a noninvasive alternative.

The study included researchers from the UCLA Center on Aging and was supported by the NIA. Small and colleagues examined 83 volunteers (middle-aged and older) to assess the ability of PET with FDDNP to identify Alzheimer's disease patients. The volunteers, who admitted to suffering memory problems, were psychiatrically evaluated and given cognitive tests. All underwent a PET scan with FDDNP, as well as FDG-PET. MRI scans were also performed on 72 of the volunteers.

Thirty volunteers were found to have no cognitive impairment, while 28 were classified as having mild cognitive impairment (MCI) and 30 as having Alzheimer's disease. When compared with FDG-PET and MRI, the PET with FDDNP method was found to be more accurate for detecting these differences.

These results demonstrated that it was possible to distinguish between healthy individuals, those with Alzheimer's disease, and those with MCI. PET with FDDNP had a 98% level of accuracy, which was higher than FDG-PET (87%) and MRI (68%). The researchers concluded that PET with FDDNP could find potential application as a noninvasive method to determine regional cerebral patterns of amyloid plaques and tau neurofibrillary tangles.

During a two-year follow-up of some volunteers, the FDDNP/PET scans continued to correlate well with clinical symptoms. "In the small number of people that we followed, we found that as the clinical symptoms get worse, the binding values increase," says Small. "So those are all features that you want to see, if something will eventually be used as a biological or surrogate marker in drug treatment trials. We still have more work to do."

Small and colleagues are moving forward in this research area. "We've obtained a program project grant from the NIA to better understand how FDDNP works in people with different cognitive impairments, to do follow-up, and to look at it in conjunction with other imaging modalities such as functional MRI and FDG-PET," he says. "Also, we have received another grant to look at it along with [F-18] MPPF, which is a marker for hippocampal neurons."

Small and colleagues are also working with Henry V. Huang, PhD, a molecular microbiologist at Washington University (St. Louis) School of Medicine, to refine their analysis approach. “We’re looking to correct for things such as head motion and to create 3D surface projections for FDDNP, which provides a strong idea of neurodegeneration.”

Looking Ahead and Inward

While recognizing the success of FDDNP in detecting amyloids, Waxman sees other tracers in the works that can have a potentially higher target-to-background ratio in patients with amyloid deposits. “Some are being looked at in patients right now,” he says.

He also points to a molecule labeled with carbon-11 called the Pittsburgh Compound B, or PIB, developed by University of Pittsburgh researchers. This compound has demonstrated success in binding amyloids in transgenic mice and, more recently, in humans. Individuals afflicted with Alzheimer’s disease typically have higher concentrations of PIB. “Right now, it’s not practical for routine use, but it has demonstrated a high degree of success in detecting amyloids,” he says. “Analogous of that particular molecule are being worked on and will probably be released for clinical testing in the near future.”

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