Molecular Imaging of Neurodegenerations

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Monday January 27, 2014
12 noon. (Please arrive early for lunch)
Brady B131 Auditorium, 310 Cedar St.

Abstract: Neurodegenerative disorders are among the most important neurologic conditions contributing to health quality and healthcare cost. Additionally, the most common disorders are age-related in incidence and prevalence, resulting in projections of steep increases in the numbers of affected individuals in the US due to increasing population age and increasing overall life expectancy. Neurodegenerative dementias are the most prevalent disorders, affecting up to 25% of those of age 80 years and older. Alzheimer disease (AD), dementia with Lewy bodies (DLB) and fronto-temporal dementias (FTD) are, in decreasing order, the most common neurodegenerative dementias. Unfortunately, our present understanding of the pathophysiological processes initiating these disorders is lacking. There are several identified genetic causes of these dementias, but they account for very few cases – the vast majorities are sporadic and not associated with identified genetic causes. Furthermore, the ability to correctly classify patients in life is imperfect. Even at subspecialty geriatric neurology and psychiatry dementia clinics, as many as 25%-33% of patients are misdiagnosed in comparison to autopsy. Thus, progress in identifying new and more effective therapies for neurodegenerative dementias is hampered by diagnostic uncertainty and mis-classification as well as by the lack of clear pathophysiologic targets.

Recent studies from our laboratories have explored the use of molecular neuroimaging to identify endophenotypes in dementia, with particular emphasis on mild, early symptomatic presentations. We employed determinations of fibrillar Aβ amyloid deposition with [11C]Pittsburgh compound-B (PiB) together with nigrostriatal dopaminergic projection integrity with [11C]dihydrorotetabenazine (DTBZ) to differentially classify patients as AD, DLB or FTD. In comparison to consensus clinical classifications, the PET endophenotyping was discordant in ~35% of cases. This result is in agreement with clinical vs. autopsy classification comparisons, and emphasizes the potential role of molecular endophenotyping in diagnosis and in the selection of subjects for therapeutic trials.

Supported by the U. S. Department of Energy, Office of Biological and Environmental Research(for infrastructure support) and the National Institutes of Health.