Epidemiologic Study of TDP-43 Pathology in Aging and Dementia

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Country

USA

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Epidemiologic Study of TDP-43 Pathology in Aging and Dementia

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5

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Epidemiology And Longitudinal Studies... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Dementia is most commonly caused by Alzheimer’s

disease (AD) pathology (plaques and tangles); however AD pathology is very commonly mixed with other pathologies which further lower cognition and increase the odds of dementia in older persons.TDP-43 pathology, a marker of an uncommon presenile dementia syndrome called Frontotemporal Lobar Degeneration (FTLD-TDP), has recently been identified in a large proportion of older brains especially those with AD pathology. The role of TDP-43 pathology in aging and AD is unknown but there is increasing evidence that it is detrimental. It is not known whether TDP-43 pathology represents a third pathology of AD or a separate coexisting disease. Our overarching hypothesis is that age-related TDP-43 pathology represents a separate pathologic process associated with a dementia syndrome with a distinct cognitive phenotype and specific genetic risk factors that are separate from AD. We propose to address these hypotheses by performing a epidemiologic study of TDP-43 pathology in aging and AD, by leveraging existing clinical, pathologic, and genetic data from 2 epidemiologic clinical-pathologic cohort studies, and collecting new TDP-43 pathology data on 1400 brains. First, using a series of analytic models, we propose to test whether TDP-43 pathology is a separate aging pathology or mediates the effects of AD pathology. Second, we propose to investigate whether TDP-43 pathology in aging is associated with a specific cognitive profile and separately increases the rate of cognitive decline. We also propose to examine the role of TDP-43 pathology in older persons without dementia, and separately examine TDP-43 in older persons without AD pathology. If TDP-43 pathology represents coexisting FTLD-TDP, the clinical profile may show early and prominent executive and language impairment rather than an AD phenotype in each of these groups. Third because the oldest-old are the fastest growing segment of the population and because AD pathology is not as relevant in this age-group, we propose to investigate the role of TDP-43 pathology in this important subgroup of older persons. Finally in the last two aims we propose to investigate the association of genetic polymorphisms (SNPs) with TDP-43 pathology and cognition. We propose that SNPs associated with FTLD are related to TDP-43 pathology in aging; whereas SNPs associated with clinical AD are related to AD pathology in aging. We present compelling preliminary data in the support of these aims. Results from these proposed studies will fill an important gap in scientific knowledge and are likely to impact future studies of prevention and treatment of cognitive impairment and dementia in aging.

Lay Summary

The number of older persons in society is rapidly expanding and creating a looming epidemic of cognitive impairment and dementia. There is compelling data that TDP-43 pathology, a recently recognized age-related pathology which often coexists with AD pathology, is strongly and separately related to cognitive impairment and dementia in the old and oldest-old. Data derived from the proposed clinical, pathologic and genetic studies of TDP-43 pathology in aging will fill an important gap in scientific knowledge and are likely to significantly alter the course of future research in the prevention and treatment of cognitive impairment and dementia in aging.

Further information available at:

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United States of America

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