Early Detection and Prevention of Alzheimer’s Disease: A white paper on groundbreaking research from Brigham and Women’s Hospital

The Science and Significance of Alzheimer’s Disease

Understanding the physiology of Alzheimer’s disease is a work in progress for medical researchers. Research conducted over the past two decades by Dennis Selkoe, MD, at Brigham and Women’s Hospital has shown that buildup in the brain of a protein called amyloid-beta is largely responsible for the degenerative effects of the disease, but there is still much to be learned. What is known is that amyloid-beta forms plaques and clumps, inhibiting the brain’s neurons and damaging their connections to one another. Other researchers are investigating the role of a protein called tau which causes “tangles” inside nerve cells, leading to the cells’ death. Though less is known about tau’s significance and its interaction with amyloid-beta, researchers are confident that the cognitive decline associated with Alzheimer’s disease is related to the processes of these two proteins.

The physical detriments of Alzheimer’s disease are seen in populations worldwide. It is estimated that some 30 million people suffer from some form of the disorder. In the United States over five million Americans, or one in nine, suffer from the stage of Alzheimer’s disease known as dementia. Estimates say that the number of Alzheimer’s patients is likely to triple in the next 20-30 years as people are living longer lives, leading Dr. Reisa Sperling, Director of the Center for Alzheimer Research and Treatment at Brigham and Women’s Hospital to call it an “epidemic of Alzheimer’s.” Existing therapies for Alzheimer’s disease often provide patients with some symptomatic relief for a short period of time; however, currently there are no treatments that change the underlying process of the disease and slow its progression.

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“... We hope to change the course of Alzheimer’s disease by starting anti-amyloid therapy earlier, before symptoms such as memory loss begin. We also expect to learn more about the factors that influence the likelihood that someone who has amyloid pathology will in fact progress towards Alzheimer’s disease dementia.”

Developments in Alzheimer’s Research

Current research is based on the fact that Alzheimer’s disease represents a continuum. That is to say, the disease progresses in stages over a long period of time. The preclinical or asymptomatic stage of Alzheimer’s disease begins more than 10-15 years before patients experience dementia. Clinical research has identified the need to distinguish between normal aging of the brain and amyloid plaque buildup in preclinical Alzheimer’s disease in order to develop an effective disease-modifying intervention. Scientists have now developed a procedure using positron emission tomography (PET) scans that can identify plaque buildup earlier in patients’ lives than ever before. This has opened doors for research and treatment before the onset of dementia.

Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease – the A4 Study

Dr. Sperling is leading a groundbreaking study, the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) Study, aimed at preventing memory loss due to Alzheimer’s disease. The A4 study is being conducted at Brigham and Women’s Hospital and 60 sites across the United States, Canada and Australia. The study will enroll 1,000 asymptomatic participants between the ages of 65-85 who are at risk of progressing to the dementia stage of Alzheimer’s disease due to evidence of abnormal amyloid protein buildup in the brain that can be detected on PET scans.

Half of these participants will be given solanezumab, an investigational anti-amyloid antibody, and the other half, a placebo. The study is a double-blind study – meaning that treatment status of each individual is unknown to patients and researchers alike, in order to strengthen the significance of the results. Participants will be studied for three and a half years using innovative methods to track the earliest stages of decline, based on clinical research conducted at Brigham and Women’s Hospital.

Dr. Sperling says that this approach draws on successful methods used with other chronic diseases.

“I think it’s very analogous to the way we treat heart disease and cancer. We’ve made such strides in these diseases by identifying people who have evidence that the disease process has begun in their bodies and starting treatment before they show any symptoms of the disease. This will be the first time we try this type of secondary prevention in Alzheimer’s disease,” she says.
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The rationale for the A4 study grew out of important research conducted at the Brigham and Women’s Hospital using PET scans, MRIs and cognitive testing, demonstrating that clinically normal individuals with evidence of amyloid plaque buildup showed evidence of subtle abnormalities in brain function and increased risk of cognitive decline. Dr. Sperling and her colleagues at Brigham and Women’s have also created a new test for memory of names and faces, that will be given on an iPad in the A4 study, that may be an even more sensitive method to detect very early memory changes.

Potential of the A4 Study

Dr. Sperling sees the A4 study as an important step in understanding and addressing the physiological processes that occur in preclinical Alzheimer’s disease over the course of time.

The design of the study is of the utmost importance. Because the participants are not exhibiting outward symptoms of Alzheimer’s disease, the trial will test whether the clinical progression of the disease can be altered in individuals with evidence of amyloid plaque buildup. Additionally, the early treatment study will allow researchers to determine what methods of detection are most likely to identify future Alzheimer’s sufferers, following a group of individuals who do not yet show evidence of amyloid buildup, in a companion study, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN). This information will be used to design future studies to prevent Alzheimer’s disease with other promising investigational agents.

If researchers see evidence of a slowed rate of cognitive decline in those participants that received anti-amyloid treatment, the A4 study could lead to the registration of a drug for preclinical Alzheimer’s disease as soon as 2019.

While the clinical results of the study are down the road, the implications of the research – led by Brigham and Women’s – are going to be extremely important to learning about the progression of Alzheimer’s disease and improving early treatment to prevent this devastating illness.