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Final Report

Elevated Homocysteine as a Risk Factor for Progression from MCI to Alzheimer's Disease

2005 Zenith Fellows Award — \$250,000 over two years

Sponsored by the Zenith Fellows and The Judy Fund

Period Covered by This Report

August 1, 2006 through July 31, 2008

Location of Research

University of Texas Southwestern Medical Center

Background

Studies have shown that elevated blood levels of homocysteine, a protein building block, may increase a person's risk of developing Alzheimer's disease. Homocysteine levels are regulated in part by the body's use of vitamin B12 and folic acid. Research has demonstrated that people with Alzheimer's often have relatively significant deficiencies in vitamin B12 and folic acid and subsequently high blood levels of homocysteine. These findings suggest a possibility that vitamin B12 and folic acid supplements may help lower the risk of developing Alzheimer's disease.

Goal of Study— Specific Aims

Ramon Diaz-Arrastia, M.D., Ph.D., and colleagues propose to assess clinical data to determine whether a high level of homocysteine in people with mild cognitive impairment (MCI) is associated with an increased Alzheimer risk. MCI is a condition that often precedes Alzheimer's. The researchers also aim to measure levels of homocysteine, vitamin B12, folic acid and related molecules in blood samples of participants from a recently completed clinical trial. In this study of 769 individuals with MCI, 212 participants developed Alzheimer's disease within three years.

Research Outcomes and Significance

During the past year, Dr. Diaz-Arrastia and colleagues have participated in several homocysteine studies. They have helped prepare a report from a research effort conducted by the Alzheimer's Disease Cooperative Study. This effort found that high-dose vitamin B therapy reduced homocysteine levels in a group of people with dementia. Further analysis found that among the

participants with early-stage dementia, the treatment showed a modest ability to slow the rate of cognitive decline.

In a second series of studies, the researchers found that vitamin B therapy was less effective at reducing homocysteine levels in older people with more advanced stages of Alzheimer's. In fact, the treatment appeared to hasten the progression of these individuals' dementia. Such results suggest that vitamin B therapy should be targeted to people with MCI and early-stage dementia, and that an alternative method should be used to reduce homocysteine levels in people with more advanced disease.

Progress on the specific goals funded by the Zenith Award has been slow, primarily due to a delay in obtaining blood samples from the MCI clinical trial. However, these samples were finally received in the spring of 2008. Dr. Diaz-Arrastia's team has completed preliminary biochemical analysis of the samples. The team will now conduct gene studies to look for possible genetic factors associated with elevated homocysteine levels and the progression from MCI to Alzheimer's disease.

Future Work

Dr. Diaz-Arrastia and colleagues have asked the Alzheimer's Association for a no-cost extension to their grant. They will use their remaining funding to continue biochemical analysis of blood samples from people with MCI. They will also use the funding to initiate their genetic studies. Collectively, these efforts should shed new light on the biochemical changes underlying Alzheimer progression.

Budget

With every peer-reviewed research grant awarded by the Alzheimer's Association, all indirect costs are capped at 10 percent (rent for laboratory/ office space is expected to be covered by indirect costs paid to the institution). The Association expects and enforces that 90 percent of the grant goes directly to funding the research itself. No more than 10 percent of the grant can be directed to administrative costs.

Approved by William H. Thies, Ph.D., Chief Medical and Scientific Officer, as a confidential communication to the Zenith Fellows. Alzheimer's Association grant ZEN-06-27450 final report.