DIMENSIONS
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FOCUS ON RESEARCH

Similarities and differences in identical twins with familial Alzheimer's disease.

By Dana Martin

Studies of identical twins with Alzheimer's disease (AD) can reveal a great deal about the disease's genetic and environmental causes. However, identical twin studies are rare and have not looked at all aspects of twin pairs to determine similarities and differences in the disease among twins. These aspects include the disease's clinical presentation (such as information gathered through exams and interviews with the family), epidemiological information (such as education level and occupation), and neuropathology (meaning examining tissue of autopsied brains).

In a recent study, ADRC researchers Dr. Thomas Bird, Dr. James Leverenz, Ellen Steinbart, Malia Rumbaugh and their colleagues, including Kiri Brickell, a neurologist from New Zealand who was completing a fellowship at the ADRC, looked at three sets of identical twins. The ADRC followed all six for a number of years. Each had, or developed, AD during the course of being studied. The diagnosis of AD was based on clinical examinations whenever possible, as well as medical records and family history. Genetics information was gathered as well, and an autopsy was performed when each twin died.

"It turns out that it's really rare in the research on Alzheimer's disease to have three complete sets of identical twins where all of them had had autopsies," says Bird. "We had an opportunity to look at the clinical, epidemiological and pathological aspects of all of them."

The goal of this study was to look at the similarities and differences between identical twins with AD to have a better understanding of how genes and the environment interact and to determine which aspects of the disease seem to be under genetic control and which seem to be influenced by environmental factors. Detailed neuropathology was performed to assess the degree of similarity and difference between each twin pair for each of these variables.

Some of the epidemiological questions the researchers asked for each twin set were if environment, education level, alcohol and tobacco use were the same or different. Clinical questions included whether age of onset and initial symptoms were the same. In terms of pathology, they examined two typical changes in the brain that are seen with AD, neuritic amyloid plaques and neurofibrillary tangles, and if those changes occurred in the same places within the brain.

Neurofibrillary Tangles

Neurofibrillary tangles are an aggregation, or clumping together, of a protein called tau. This change occurs within brain cells. These aggregated tau proteins form long, twisted fibers.

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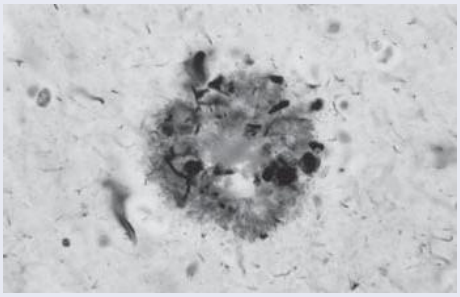
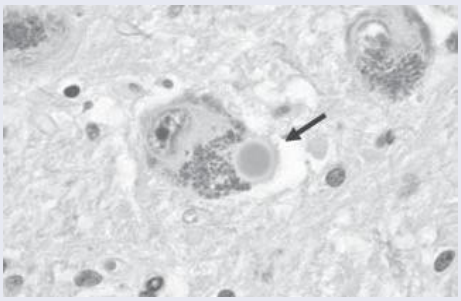


Neuritic Amyloid Plaques

Neuritic amyloid plaques are changes outside the cells but within the brain tissue. These plaques contain the protein that most people are very interested in as a cause of Alzheimer's disease, called amyloid.

"It's the presence of both the plaques and tangles that is required to make a diagnosis of Alzheimer's disease," says Leverenz. "There are some diseases in which you have only the tangles, and that's another disease altogether, not Alzheimer's disease."



Lewy Body

The study also looked at whether both twins in each pair had Lewy bodies. Lewy bodies are changes in the brain associated with Parkinson's symptoms, and they are found in about half of patients with AD.

Dr. Leverenz underscores the importance of neuropathy in understanding AD, particularly the presence or absence of Lewy bodies. "There are things that we just can't tell about the characteristics of the disease by looking at the patient clinically, such as the presence of the Lewy bodies," he says. "When we look at those people with coexistent Lewy bodies, there do seem to be some unique clinical characteristics, but they're fuzzy enough that accuracy based purely on a clinical history, characteristics and examination is not as accurate. Neuoropathological examination improves the accuracy of the characterization of the dementia that the person has."

The study had several important findings. It confirmed that genetics play a strong role in AD. Both neuritic amyloid plaques and neurofibrillary tangles were nearly identical in each twin pair in terms of numbers and locations. Clinically, each twin pair was very similar as well.

However, the study also found that genetics is not the whole story. Age of onset varied considerably, with a difference of between 4 and 18 years within each twin set. Also, in two of the three twin pairs, the twin with the later age of onset did not have Lewy bodies. It appears that disease duration is highly correlated with whether Lewy bodies are present.

"We came to the conclusion that, in these cases, genetics was driving a lot of the clinical and pathological characteristics of the disease but was not in control of everything," Bird says. "There must have been other factors that were playing some role in age of onset, and there probably are other factors playing a role in whether they develop the Lewy bodies or not."

This study is the first to look at the presence of Lewy bodies in identical twins, and the findings provide another piece of evidence that the Lewy bodies, although they are important in Alzheimer's disease, may not be as correlated with the genetics driving the disease as other changes such as the plaques and tangles. "This allows us to begin to think a little bit differently about the Lewy bodies and their relationship to the pathology," Bird says.

Another finding was that one twin pair had a mutation in PS1, known as the A79V mutation. A brother of the twins had remarkably late onset, having been diagnosed at 79 years of age. This is interesting because PS1 mutations are associated with early-onset AD. This relative represents the oldest age of onset in a person with the A79V PS1 mutation.

At this point, it's not clear what environmental factors influence age of onset for AD. The backgrounds of each twin pair were similar. They all had high school educations, grew up in the same environments and had similar professions. Dr. Bird points out that ideas about what environmental factors might be at play aren't well-formulated, and more research is needed to determine what these factors are. He says, "If we knew what could delay the onset of the disease, that would be

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a treatment."

This study also shows how valuable it is for those with Alzheimer's and their families to be involved in this research for the long term. Dr. Bird thanks all these families for donating so much of their time, as well as blood and tissue samples, for this research. It could not be accomplished without them.

If you are interested in participating in genetic studies of Alzheimer's disease, please contact Ellen Steinbart at 206-764-2112 or toll free at 1-800-745-4511.

The results of the study are published in the *Journal of Neurology, Neurosurgery & Psychiatry,* Vol. 78, 2007. ❖

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Dr. Linda Teri gives Lawton award lecture at the 60th Annual GSA Meeting.

The Gerontological Society of America (GSA) held its 60th Annual Scientific Meeting Nov. 16-20 in San Francisco. The theme was "The Era of Global Aging: Challenges and Opportunities." A highlight of this year's conference was the Lawton Award Lecture, delivered by University of Washington Alzheimer's Disease Research Center faculty member Dr. Linda Teri.

Drs. Linda Teri with Nancy Fugate Woods, Dean of the University of Washington School of Nursing

Dr. Teri provided an overview of 20 years of research on identifying and treating behavioral problems in Alzheimer's disease (AD). She described the development of psychosocial treatments to treat these problems, meaning treatments that look at the interaction between social and psychological factors.

In her lecture, Dr. Teri noted that research has come a long way in the past two decades. Just 20 years ago, it was believed nothing could be done to help people with AD – that they would simply have to suffer and worsen as the illness progressed. Now, clinicians have a variety of research-based interventions shown to improve care and quality of life for those living with AD, as well as their caregivers.

In particular, Dr. Teri noted that co-existing emotional and behavioral disturbances cause "excess disability" over and above the cognitive decline that occurs in dementia. In the 1980s, Dr. Teri and colleagues conducted a series of clinical investigations applying behavioral and social learning theory to the treatment of depression in AD. These studies showed that training caregivers to use behavioral skills to increase pleasant events and decrease negative behaviors was as effective as antidepressant medicine in treating depression in the person with AD.

The use of behavioral skills also improved the caregiver's mood. The effects of the treatment were long-lasting: They persisted even after the nine-week treatment program was completed.

Dr. Teri also talked about the role of exercise in reducing excess disability in AD. A 2003 study involving exercise along with behavioral management that lasted 12 weeks and had an exercise and problem-solving focus showed significant decreases in depression at three-month and two-year follow-up.

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