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Alzheimer's Precursors Evident in Brain at Early Age

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Scientists studying Alzheimer's disease are increasingly finding clues that the brain begins to deteriorate years before a person shows symptoms of dementia.

Now, research on a large extended family of 5,000 people in Colombia with a genetically driven form of Alzheimer's has found evidence that the precursors of the disease begin even earlier than previously thought, and that this early brain deterioration occurs in more ways than has been documented before.

The studies, published this month in the journal Lancet Neurology, found that the brains of people destined to develop Alzheimer's clearly show changes at least 20 years before they have any cognitive impairment. In the Colombian family, researchers saw these changes in people ages 18 to 26; on average, members of this family develop symptoms of mild cognitive impairment at 45 and of dementia at 53.

These brain changes occur earlier than the first signs of plaques made from a protein called beta amyloid or a-beta, a hallmark of Alzheimer's. Researchers detected higher-than-normal levels of amyloid in the spinal fluid of these young adults. They found suggestions that memory-encoding parts of the brain were already working harder than in normal brains. And they identified indications that brain areas known to be affected by Alzheimer's may be smaller than in those who do not have the Alzheimer's gene.

"This is one of the most important pieces of direct evidence that individual persons have the disease and all the pathology many years before," said Dr. Kaj Blennow, a professor in clinical neurochemistry at the University of Gothenburg in Sweden, who was not involved in the research.

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Dr. Nick Fox, a neurologist at University College London, who was also not part of the research, said the findings suggested that "some of the things that we thought were more downstream may not be quite so downstream; they may be happening earlier."

That, in turn, said Dr. Fox, who wrote a commentary about the findings in Lancet Neurology, could have implications for when and how to treat people, because "there may be targets to attack, whether it's high levels of a-beta or whatever, when people are still functioning very well."

The Colombian family suffers from a rare form of Alzheimer's that is caused by a genetic mutation; it strikes about a third of its members in midlife. Because the family is so large and researchers can identify who will get the disease, studying the family provides an unusual opportunity to learn about Alzheimer's causes and pathology.

Researchers, led by Dr. Eric Reiman of the Banner Alzheimer's Institute in Phoenix, and in Colombia by Dr. Francisco Lopera, a neurologist at the University of Antioquia, recently received a grant from the National Institutes of Health to conduct a clinical trial to test a drug on family members before they develop symptoms, to see if early brain changes can be halted or slowed.

The studies in Lancet Neurology used several tests, including spinal taps, brain imaging and functional M.R.I.

"The prevailing theory has been that development of Alzheimer's disease begins with the progressive accumulation of amyloid in the brain," Dr. Reiman said. "This study suggests there are changes that are occurring before amyloid deposition."

One possibility is that brain areas are already impaired. Another possibility, experts said, is that these brain differences may go back to the young developing brain.

"It is a genetic disease, and it's not hard to imagine that your gene results in some differences in the way your brain is formed," said Dr. Adam Fleisher, director of brain imaging at the Banner Institute and an author of the studies.

In one of the Lancet Neurology studies, researchers examined 44 relatives between ages 18 to 26. Twenty had the mutation that causes Alzheimer's. The cerebrospinal fluid of those with the mutation contained more amyloid than that of relatives without it. This was striking because researchers know that when people develop amyloid plaques — whether they have early-onset or late-onset Alzheimer's — amyloid levels in their spinal fluid are lower than normal. That is believed to be because the fluid form of amyloid gets absorbed into the plaque form, Dr. Reiman said.

So, the high level of amyloid fluid in the Colombian family supports a hypothesis about a difference between the beginning phases of genetic early-onset Alzheimer's and the more common late-onset Alzheimer's. The difference may be that early-onset Alzheimer's involves an overproduction of amyloid, while late onset involves a problem clearing amyloid from the brain.

In another result, when the subjects performed a task matching names with faces, those with the mutation had greater activity in the hippocampus and parahippocampus, areas involved in memory. Dr. Reiman suggested this could mean that the pre-Alzheimer's

brain has to expend more effort to encode memories than a normal brain.

Researchers also found that the mutation carriers had less gray matter in areas that tend to shrink when people develop dementia. Dr. Fox emphasized that seeing less gray matter so early was so novel that it should be treated cautiously unless other studies find a similar result.

In the second study, brain imaging was used to look for amyloid plaques in 50 people ages 20 to 56: 11 with dementia, 19 mutation carriers without symptoms and 20 normal family members. Plaques occurred at an average age of 28, more than 15 years before cognitive impairment would be expected and two decades before dementia.

The study also found that amyloid plaques increased steadily until about age 37, after which the brain did not seem to gain many more plaques. Dr. Blennow said that while researchers know that amyloid plaques plateau when people already have dementia, they did not know that the plateau appears to occur years before.

The researchers are currently analyzing data from family members ages 7 to 17 to see if some of the brain changes occur at an even younger age.

“Some people think that that may be scary, that you can see it so many years before,” Dr. Reiman said. “But it seems to me that that provides potential opportunities for the development of future therapies.”