NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Microglial Activation Reduces AD's Signs, Symptoms in Mouse Model

This month's column explores the dynamic area of immunotherapy for Alzheimer's disease. Although the research is based on a mouse model, it employs a novel strategy that could rapidly translate to human clinical trials based upon the availability and current use of the proposed agent.

RICHARD J. CASELLI, M.D.

Chronic treatment with macrophage-colony stimulating factor can prevent and treat learning and memory deficits as well as β-amyloid pathology in a mouse model of Alzheimer's disease without causing any detectable toxicity, according to new research.

Vincent Boissonneault of Laval University, Quebec City, and his colleagues used macrophage-colony stimulating factor (M-CSF) to promote the proliferation and activation of microglia in the central nervous system and bone marrow. When activated, these microglia can differentiate into macrophagelike cells that are known to be attracted to aggregates and plaques of β-amyloid (Aβ).

"While some studies have demonstrated that in some circumstances, microglia can be detrimental in the Alzheimer's disease brain, many others have supported the theory that they are actually beneficial," the researchers wrote in their report (Brain 2009 Jan. 17 [doi:10.1093/brain/awn331]).

Weekly intraperitoneal injections of murine M-CSF in transgenic mice aged 2-6 months prevented them from developing signs of social withdrawal and cognitive impairment at ages 6 and 9 months. These transgenic mice, which express a chimeric human-mouse Aβ precursor protein gene and the human presenelin-1 gene, normally begin to display Alzheimer's disease–like behavioral abnormalities and Aβ pathology at around age 6 months.

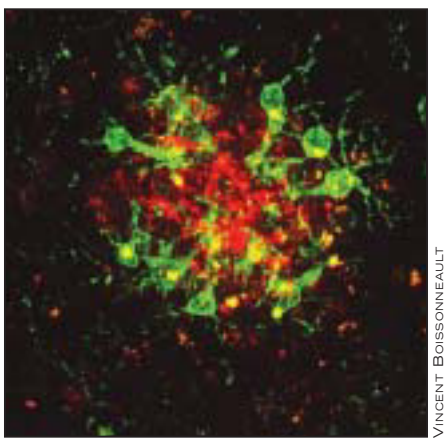
In another experiment with mice that were already showing these abnormalities, treatment with M-CSF at ages 6-9 months reversed learning and (spatial and nonspatial) memory deficits in 39% of mice. The disease stabilized in an additional 39% of the mice after the treatment.

The treatment also significantly reduced Aβ deposits in the brains of transgenic mice, including fewer Aβ monomers and less dense plaques, which were often devoid of microglia. The cortices and hippocampi of these mice had more than twice the number of microglia than that of their saline-treated transgenic littermates. Most of these microglia were derived from bone marrow.

In mice that received M-CSF, significantly more of the microglia in these regions contained Aβ, often in its fibrillar form. Significantly lower levels of Aβ monomers, particularly Aβ42, were detected in the extracellular fraction of mice that received M-CSF. Other evidence suggested that these bone marrow-derived microglia may clear Aβ through endocytosis and lysosome-mediated degradation.

All three known hematopoietic cytokines have been implicated in the development and progression of some inflammatory and autoimmune disorders in humans. Previous studies in microglial cell cultures that were stimulated with M-CSF have demonstrated increases in proinflammatory cytokines when exposed to Aβ, but the investigators visually evaluated the morphology of the M-CSF-treated mice's organs and found no signs of detrimental inflammatory effects such as encephalitis or vasculitis. Mr. Boissonneault and his colleagues acknowledged that future studies in mice (and potentially in humans) would require a detailed histologic analysis of the organs and a closer search for inflammation and systemic immunologic dysfunction.

"Since this cytokine has been tested in humans to stimulate the hematopoietic system, it is conceivable to propose its use as a new treatment for Alzheimer's disease," the researchers wrote.



VINCENT BOISSONNEAULT

Beta-amyloid (red) is surrounded and in some cases internalized by microglia (green) in a brain slice from a transgenic mouse treated with M-CSF.

***Dr. Caselli's comment*:** Since the first demonstration of vaccine-mediated amyloid plaque clearing in transgenic mice by Dr. Schenk and colleagues (Nature 1999;400:173-7), immunotherapy for Alzheimer's disease has been an area of intense investigation. Early enthusiasm, however, was dimmed by the occurrence of a vaccine-induced autoimmune meningoencephalitis and vasculitis occurring in roughly 6% of patients treated in the AN1792 trial (Neurology 2003;61:46-54).

But autopsy studies of treated patients have shown evidence of plaque clearing (Nat. Med. 2003;9:448-52), and newer strategies—including active vaccines that do not provoke a T-cell response, passive immunization, as well as a variety of alternative antiamyloid strategies (antiaggregants, secretase inhibitors, and others)—have reached clinical trial stages, although to date there have been no reports of major therapeutic successes.

The study by Mr. Boissonneault and associates employs a different immunologic strategy that still results in highly effective plaque clearing as well as demonstrated behavioral benefits in the double-transgenic APP-PS1 mouse. What is perhaps most exciting is that the agent utilized is one that has already been tested in human trials (Lancet 2009;373:188-90), and generally found to be safe. The patient populations in which it has been tested, however, are generally very different (typically much more acutely ill) than the typical Alzheimer's disease patient, and so it is difficult to know whether trials in the latter group will generate similarly propitious safety and tolerability profiles. Subsequent follow-up of vaccine-treated Alzheimer's patients has shown that plaque clearing was not accompanied by altered clinical course (Lancet 2008;372:216-23), raising the possibility that even if M-CSF successfully clears plaques in patients with established dementia, it may not result in reversing cognitive loss or even attenuating further decline.

Many investigators have appropriately suggested that earlier intervention, before the disease process has firmly established its degenerative cascade, would be more likely to succeed, and the feasibility of a trial in patients with mild cognitive impairment, as proposed by Mr. Boissonneault and colleagues, offers yet another exciting glimmer of hope. ■

Clinical perspective by Dr. Caselli, chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.

Research report by Jeff Evans, senior writer.

Midlife Diabetes Diagnosis Doubles Risk of Dementia

BY HEIDI SPLETE
Senior Writer

A midlife diagnosis of diabetes increases the risk of developing Alzheimer's disease and vascular dementia, based on results of a twin study including more than 13,000 individuals.

Previous studies have shown that people with diabetes are at increased risk for dementia, but little is known about the mechanism of action, wrote Dr. Weili Xu of the Karolinska Institutet, Stockholm, and the Stockholm Gerontology Research Center.

Dr. Xu and colleagues conducted this twin study to verify the effect of diabetes on dementia, examine whether this effect varied based on the age of diabetes onset, and assess the possible role of genetics (Diabetes 2009;58:71-7). Data were taken from a national registry of Swedish twins who were at least 65 years old when they entered the study between 1998 and 2001.

Of 13,693 participants, 13,056 had no dementia, 467 had dementia, and 170 had questionable dementia, based on DSM-IV criteria. Midlife diabetes was defined as the onset of type 2 diabetes before age 65 years.

A total of 1,396 individuals had type 2 diabetes; 643 developed diabetes before age 65, and 753 developed diabetes at age 65 or older.

Overall, diabetes was significantly associated with a higher risk of dementia, and patients whose diabetes was diagnosed at midlife were more than twice as likely to develop dementia as those diagnosed later in life, even after controlling for diabetes duration and twin factors. In an analysis using a generalized estimating equation model (to measure all subjects at a common set of times) midlife and late-life diabetes diagnoses were significantly associated with increased dementia risks of 176% and 63%, respectively.

In addition, data from co-twin matched case-control analyses showed that the effect of midlife diabetes on dementia remained significant while the effect of later-life diabetes diagnosis on dementia did not.

These data suggest that adult lifestyle traits such as diet, exercise, smoking, and diabetes control may have a substantial impact on the link between midlife diabetes and dementia.

But "unmeasured familial factors" including genetic factors and environmental influences in early life might contribute to the association between late-life diabetes diagnosis and dementia, the researchers noted.

The study's limitations include the prevalence of dementia cases, the use of self-reports, and the lack of information about genes and environmental factors.

However, the findings "add to the growing evidence of a link between diabetes, vascular damage, and neurodegenerative changes in the brain," they wrote, adding more studies are needed to identify environmental factors and genetic influences.

The study was supported in part by research grants from sources including the National Institute on Aging and the American Alzheimer's Association. The researchers disclosed no financial conflicts of interest. ■