DISEASE MECHANISMS

Why Carotid Stenosis May Portend Future Brain Atrophy and Cognitive Decline

BY JAMIE TALAN

ARTICLE IN BRIEF

Researchers reported an association between carotid atheroma and the structure of the cerebral cortex in people, ages 73 and older, who had been followed since childhood.

Blockage of the carotid arteries, even small amounts of stenosis thought to be normal in older people, could presage brain atrophy and cognitive problems. And the finding is independent of common risk factors for vascular disease, according to Canadian scientists who reported their findings in the September 4 issue of *Annals of Neurology*.

Simon Ducharme, MD, and his colleagues at the Montreal Neurological Institute and the University of Edinburgh, wanted to understand the connection between vascular risk factors, cognitive decline, and cortical atrophy. They worked with data from a rare cohort of men and women from a small village in Scotland who had extensive cognitive testing at 11 years old, and then extensive medical, imaging, and cognitive testing 62 years later.

DR. SIMON DUCHARME: "What's important is that the association between stenosis, carotid thinning, and deficits in cognitive performance is not the result of hypertension and other vascular risk factors, or how someone performed on an IQ test at the age of 11 years old. We need to pay more attention to even mild stenosis. It is telling us something important about what is going on in the brain."

In their analysis, the researchers found that carotid stenosis was associated with brain atrophy, which had negative consequences on cognition.

"Even small degrees of carotid stenosis that clinicians would call normal were linked to decreased cognitive performance," Dr. Ducharme told *Neurology Today*. "We think that this could be an early marker for vascular problems in the brain, and clinicians should take this seriously and help patients improve their vascular health."

STUDY METHODS, FINDINGS

Their analysis was based on a longitudinal study of 70,000 children born eleven years earlier in Scotland who were part of a countrywide program to collect IQ scores.

Between 2004 and 2007, about a thousand of the adults in Lothian took part in follow-up extensive medical and cognitive testing. They were around 70 at the time. Several years later, from 2007 to 2010, a second wave of testing was done. This time, 866 study participants underwent brain magnetic resonance

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Blocking Fibrin Signaling, MS and AD Models

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reduced neurologic signs when given prophylactically; when given after disease onset, treatment reduced relapses, and only 25 percent of the mice developed paralysis versus more than 75 percent of mice receiving a control antibody. Treatment reduced microglial activation and damage to spinal cord axons.

The 5XFAD double transgenic mouse is a model for severe AD in which fibrin can be detected in the brain within three months of birth. Treatment with 5B8 beginning at 3.5 months reduced the loss of cholinergic neurons and reduced the concentration of activated microglia around amyloid-beta plaques, but it did not reduce the number of plaques themselves. Dr. Akassoglou has not yet tested the effects of treatment on cognition but noted this is a key question for future research.

"More work will be needed to better characterize this antibody," Dr. Akassoglou cautioned, "but the ability to target innate immunity in either MS or AD could represent an important therapeutic strategy," she said. "Innate immunity has many protective functions, so a challenge in the field has been that a global shutdown of the innate immune response is unlikely to be clinically viable. But we think there might be room for ligand-selective targeting as an alternative. This approach could be especially valuable for neutralizing the toxic effects of the blood in the brain in neurological diseases with vascular abnormalities and blood-brain barrier leakage."

DR. COSTANTINO IADECOLA: "Fibrin is not the sole contributor, of course, but it may be a really important contributor, and that would make it worth targeting. Dr. Akassoglou has been a pioneer in pushing this idea forward. However, this strategy absolutely has the same challenges as other antibody-based therapies and is likely to be only one aspect of a multi-pronged approach to slow neurodegeneration."

The ideal timing and duration of therapy are still unclear, she added. But she pointed out that the normal mechanisms for removal of fibrin, and therefore reduction of the pathogenic signaling, are impaired in many neurologic diseases, and so may result in a chronic inflammatory response even after the blood-brain barrier has been repaired.

"Neuropathology suggests that clotted fibrin may remain in the brain for a long time," she said, which may require prolonged treatment to continue blockade of the inflammatory signal.

EXPERT COMMENTARY

"This research is a step in the right direction to understand the constellation of contributors to neuroinflammation in both multiple sclerosis and Alzheimer's disease," commented Costantino Iadecola, MD, professor of neurology and director of the Feil Family Brain and Mind Research Institute at Weill Cornell Medicine in New York. "Fibrin is not the sole contributor, of course, but it may be a really important contributor, and that would make it worth targeting. Dr. Akassoglou has been a pioneer in pushing this idea forward."

"However," he noted, "this strategy absolutely has the same challenges as other antibody-based therapies and is likely to be only one aspect of a multi-pronged approach to slow neurodegeneration."

Finally, he cautioned, the degree of benefit that could be expected from even an effective anti-fibrin strategy may be patient-specific, since the mix of pathogenic factors may differ from patient to patient.

Dr. Steinman, of Stanford, commented, "This work is exquisitely detailed, and I think it has big implications, but the challenge is targeting fibrin safely. It is a pathway that is underexplored for very good reasons — as soon as you start modulating clotting, you have the potential for unwanted bleeding or coagulation. The antibody may be dramatically useful, but someone will have to work up the courage to try it. I think bringing this approach forward is possible, but those are the issues that will have to be overcome." •

LINK UP FOR MORE INFORMATION:

- Ryu JK, Rafalski VA, Meyer-Franke A, et al. Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration. *Nat Immunol* 2018;19(11):1212-1223.

Carotid Stenosis, Cognitive Problems

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imaging, and 820 of them had a carotid artery Doppler ultrasound. They all had repeated clinical and cognitive tests, including the Mini-Mental State Examination to screen for dementia.

Dr. Ducharme, who studies Alzheimer's disease and frontotemporal dementia, analyzed the data to determine whether cortical thickness mediates the association between carotid atheroma and cognitive decline.

The analyses included information from both imaging scans (with good resolution) plus medical history and clinical data from 554 study participants — 296 men and 258 women. The researchers wanted to assess the impact of aging, medical history, and behavioral factors on brain health.

The researchers looked at carotid atherosclerosis markers and cerebral cortical thickness. They controlled for gender, known vascular risk factors such as hypertension and diabetes, and the study participants' IQ results at age 11. They also looked to see whether there was a relationship between carotid stenosis and the cognitive testing of fluid intelligence that they collected at age 73.

The investigators identified a widespread negative association between carotid stenosis and cerebral cortical thinning within the anterior and posterior circulation territories. This was true independent of the side of the stenosis or carotid measures, vascular risk factors, and the participants' childhood IQ scores. The association was stronger with more moderate to severe degrees of carotid stenosis but was present even at the lowest degree of stenosis.

There was also a statistically strong negative association between stenosis and fluid intelligence. This association was present even when they controlled for a history of hypertension, hypercholesterolemia, diabetes, smoking, or a history of stroke and/or coronary heart disease. About 22 percent of the effect of carotid stenosis on fluid intelligence was mediated by cortical thickness, said Dr. Ducharme.

Fifteen percent of the study participants had no carotid stenosis and almost 30 percent had 25- to 49-percent stenosis. Four percent of the subjects had greater than 50 percent blockage. Even those with mild stenosis had widespread bilateral cerebral cortical thinning and lower performance on a number of cognitive tests, he added.

While diabetes and smoking were linked to cortical thinning, hypertension, hypercholesterolemia, and body mass index were not. Even stenosis in one carotid artery was associated with bilateral cortical thinning in prefrontal, parietal, and lateral temporal brain region.

The mechanism responsible for this association is not clear. Dr. Ducharme said that compromised blood flow doesn't explain the finding. Stenosis less than 50 percent does not cause problems with blood flow. He thinks that carotid stenosis is a marker for vascular problems in the brain.

"What's important is that the association between stenosis, carotid thinning, and deficits in cognitive performance is not the result of hypertension and other vascular risk factors, or how someone performed on an IQ test at the age of 11 years old," he added. "We need to pay more attention to even mild stenosis. It is telling us something important about what is going on in the brain."

DR. JULIE A. SCHNEIDER: "These findings confirm the importance of atherosclerosis in both brain health and cognition. It also may tell us something about mechanisms. Both vascular disease and Alzheimer's disease may be related to cortical volume loss, so it will be important to follow this up with pathologic studies to investigate whether the underlying brain pathology is amyloid and tangles (Alzheimer's disease pathology) or vascular (macro or microinfarcts)."

EXPERT COMMENTARY

"It's not surprising that carotid stenosis would be related to cortical thickness, but I am surprised it would be related to cortical thickness in the absence of white matter hyperintensities," said Julie A. Schneider, MD, the Deborah R. and Edgar D. Jannotta presidential professor of pathology and neurological sciences, and associate director at the Rush Alzheimer's Disease Center at Rush University Medical Center.

"These findings confirm the importance of atherosclerosis in both brain health and cognition," Dr. Schneider said. "It also may tell us something about mechanisms. Both vascular disease and Alzheimer's disease may be related to cortical volume loss, so it will be important to follow this up with pathologic studies to investigate whether the underlying brain pathology is amyloid and tangles (Alzheimer's disease pathology) or vascular (macro or microinfarcts). The mechanism will help us understand the role of atherosclerosis in human brain diseases of aging, especially Alzheimer's disease and vascular disease.

"If confirmed, this may suggest that treating both moderate and severe degrees of carotid stenosis may be beneficial as a preventive measure of cognitive decline," Dr. Schneider continued. "But first, it will be important to replicate the findings of this study and to consider risk vs. benefit of carotid surgery, which itself can have morbidity. If indicated, clinical trials would be the ideal mechanism to confirm of the value of an intervention. More work is needed to determine the mechanisms involved in promoting this risk."

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"There have been quite a few studies exploring the association between carotid artery disease and measures of brain health (including cortical thickness, resting blood flow, reactive blood flow, functional MRI studies)," said Eric McDade, DO, associate professor of neurology at Washington University School of Medicine.

But this study is unique because the researchers were able to use a measure of intelligence collected from the birth cohort during childhood, Dr. McDade said. "This has been used as a proxy of cognitive reserve during aging. The researchers were able to account for this measure of cognitive reserve when they looked at the association between carotid artery disease, brain volume, and cognitive performance in the eighth decade of life.

DR. ERIC MCDADE: "As we increasingly move towards strategies in preserving brain health in aging this study suggests that a relatively simple test, carotid ultrasound, could be used to provide important information on someone's risk of developing cognitive decline."

"As we increasingly move towards strategies in preserving brain health in aging this study suggests that a relatively simple test, carotid ultrasound, could be used to provide important information on someone's risk of developing cognitive decline," Dr. McDade continued.

The findings "suggest effects are associated with vascular disease that may be occurring long before severe vascular disease is identified. Because carotid ultrasound is relatively easy to obtain it could be used as a proxy to screen for relevant levels of cerebrovascular disease that are not otherwise easy to obtain or detect.

"If confirmed in other large, population-based studies with a greater ethnic diversity it is conceivable that this type of information could be implemented into midlife health screens," Dr. McDade said. "What would be important to explore is whether the brain atrophy is reversible following interventions (pharmacologic and non-pharmacologic) with decreasing levels of carotid artery disease." •

DISCLOSURES

Dr. Ducharme received travel-related expenses from the Ionis Pharmaceutical company for an advisory meeting, but this is not related to this study. Drs. Schneider and McDade reported no related disclosures.

LINK UP FOR MORE INFORMATION:

- Alhusaini S, Karama S, Nguyen TV, et al. Association between carotid atheroma and cerebral cortex structure at age 73 years. *Ann Neurol* 2018; 84: 576-587.