Blood-Brain Barrier Breakdown: Early Dementia Biomarker

Damian McNamara

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Increases in a marker indicating damage to vascular cells that help maintain the blood-brain barrier (BBB) are associated with greater risk for cognitive impairment, suggesting a separate physiologic path to Alzheimer's disease (AD) and other dementias, new research suggests.

In the cross-sectional study, not all brain regions were affected equally. The degradation of brain capillary pericyte cells occurred most prominently in the hippocampus and related structures of the brain.

Importantly, the findings were independent of traditional signs of dementia risk.

"Vascular dysfunction reflecting loss of cerebrovascular, blood-brain barrier integrity in the hippocampus is an early biomarker of human cognitive dysfunction independent of classical Alzheimer's biomarkers: amyloid-beta or tau," senior author Berislav V. Zlokovic, MD, PhD, chair of AD research, director of the Zilkha Neurogenetic Institute, and professor and chair of the Department of Physiology and Neuroscience, Keck School of Medicine, University of Southern California (USC), Los Angeles, told *Medscape Medical News*.

"Treating vascular BBB breakdown and leaky blood vessels holds potential to delay and/or arrest cognitive decline, irrespective of whether the individuals have positive or negative classical Alzheimer's biomarkers," Zlokovic added.

The findings were published online January 14 in *Nature Medicine.*

Unrecognized Biomarker

The study is "important because it shows that this is a separate, previously unrecognized correlate of cognitive impairment," noted co-investigator Daniel A. Nation, PhD, also from the Department of Physiology and Neuroscience at USC.

"If you're only measuring traditional vascular factors, you wouldn't be able to pick up on this other phenomenon linked to cognitive impairment in this population," Nation told *Medscape Medical News.*

The biomarker in question, platelet-derived growth factor receptor-β (*PDGFRβ*), is primarily expressed by brain vasculature cells, which makes it more specific to BBB breakdown. Neurons, astrocytes, endothelial cells, oligodendrocytes, and/or microglia do not express this factor.

In addition, previous research suggests that increased soluble *PDGFRβ* in cerebrospinal fluid (CSF) correlates with greater BBB dysfunction on dynamic contrast-enhanced MRI in patients with mild cognitive impairment.

For the study, the investigators assessed 161 adults aged 45 years and older with no cognitive dysfunction or early cognitive decline on neuropsychological testing. They enrolled 74 participants in California and another 87 at Washington University in St. Louis, Missouri, and measured soluble *PDGFRβ* in CSF.

A subgroup of 35 participants also underwent PiB-PET imaging for amyloid-β. Another cohort of 73 participants underwent dynamic contrast enhanced (DCE) MRI.

Participants were stratified as either negative or positive for the presence of amyloid-beta (Aβ) or phosphorylated Tau (pTau) based on CSF assays.

The researchers found increased CSF soluble *PDGFRβ* was associated with more advanced Clinical Dementia Rating impairment (CDR 1 > 0.5 > 0). This suggests progressive damage of pericytes with greater cognitive dysfunction.

Independent Mechanism

They also observed increased soluble *PDGFRβ* in participants with CDR 0.5 relative to CDR 0 scores, regardless of whether they were positive or negative for Aβ or pTau. This finding, again, suggests a mechanism independent of detectable neuronal degeneration.

In addition, DCE-MRI showed differences between CDR 0.5 and CDR 0 groups in brain regions of interest.

For example, those with scores indicating more cognitive impairment had increased BBB permeability. This was shown using a gadolinium-based contrast agent in the hippocampus and its CA1, CA3, and dentate gyrus subfields, as well as in the parahippocampal gyrus.

Furthermore, higher CSF soluble *PDGFRβ* remained a significant predictor of cognitive impairment after statistically controlling for CSF Aβ 42 and pTau, according to analysis of covariance (ANCOVA) models.

Soluble *PDGFRβ* levels in CSF also correlated with classical biomarkers of BBB breakdown, including CSF/plasma albumin ratio and CSF fibrinogen, further supporting the utility of this biomarker.

In contrast, the frontal and temporal cortex, subcortical white matter, corpus callosum, internal capsule, and deep gray matter regions including the thalamus and striatum did not feature such DCE-MRI differences.

ANCOVA analyses showed that increased regional BBB permeability in the hippocampus, parahippocampal gyrus, and hippocampal subfields remained a significant predictor of cognitive impairment even after controlling for CSF Aβ 42 and pTau.

"These are brain regions that have been implicated in AD for a very long time," Nation said. These regions underpin a number of cognitive functions, including episodic memory.

The investigators also evaluated several cognitive domains using normalized scores from 10 neuropsychological tests.

Biomarkers of Early Decline

Compared with participants with no domain impairment, those with an impairment in memory, attention/executive function and language, or global cognition were more likely to have elevated levels of the biomarker.

Analogous to the CDR results, and after statistically controlling for amyloid levels, the participants who underwent PiB-PET scans and had one domain impairment also showed increased CSF soluble *PDGFRβ* relative to those without impairment.

There were no differences in CSF markers of glial and/or inflammatory response or neuronal degeneration between impaired and unimpaired participants based on neuropsychological testing.

In addition, patient age did not significantly alter the CSF soluble *PDGFRβ* or DCE-MRI findings between CDR 0.5 and CDR 0 cohorts.

"These data indicate that CSF soluble *PDGFRβ* and hippocampal and parahippocampal gyrus BBB measures reflect cognitive impairment independent of normal aging. Therefore, they may be good biomarkers of early cognitive dysfunction," the investigators write.

Zlokovic and team coincidentally published two other studies this month, one in animals and one in patients.

The study in mice, which was published in the *Journal of Experimental Medicine,* showed that a genetically modified human blood protein called 3K3A-APC, in development for stroke treatment, could also play a protective role against Aβ deposition in AD.

The second study, published in the *Annals of Neurology,* looked at the potential of 3K3A-APC in combination with tPA, mechanical thrombectomy, or both in 110 patients with moderate-to-severe acute ischemic stroke. This phase 2 RHAPSODY trial supports a neuroprotective role of the protein for lower hemorrhage rates in this population, the

investigators note.

"RHAPSODY Phase 2 has shown that 3K3A-APC is safe in stroke patients that normally develop a high degree of BBB breakdown. This trial also showed that 3K3A-APC limits incidence of bleeding in the brain after tPA or thrombectomy in patients with stroke by 67% and reduces by more than 60% volume of hemorrhages in the brain in these patients by protecting the vascular system," said Zlokovic.

Unanswered Questions

The potential connection between the two studies could be that 3K3A-APC may also be helpful in treating microhemorrhages in patients with mild cognitive impairment and/or early AD that develop in more than 70% of cases, Zlokovic added.

The timing in the current study remains a mystery. How loss of the BBB integrity "fits in with amyloid and tau over time or over the course of Alzheimer's disease — that is the part that is still unknown," Nation said.

In other words, because the current study was cross-sectional, the investigators could not address any temporal relationship.

"There are a lot of questions that can only be answered in a longitudinal study, which we are doing," Nation added.

Future longitudinal research could help to establish the role of BBB breakdown as a predictor of human cognitive decline in individuals at genetic risk for Alzheimer's, Zlokovic said.

In addition, the researchers would like to progress to Phase 3 studies with 3K3A-APC for stroke and Phase 2 studies for amyotrophic lateral sclerosis (ALS). "These are our clinical aspirations," he added.

"On a more fundamental level, we want to understand better molecular and cellular mechanisms in the cerebrovascular system leading to brain vascular failure and damage causing dementia and Alzheimer's," Zlokovic said. "The ultimate goal is to develop new treatments for these devastating disorders of the human brain."

"The other thing we're examining is the role of the *APOE*E4* allele, which we have a lot of reason to suspect is important in blood-brain barrier breakdown," Nation said. "That will also be forthcoming."

Strong Evidence

Commenting on the findings for *Medscape Medical News,* Veronica Galvan, PhD, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases and associate professor of cellular and integrative physiology at the University of Texas Health San Antonio, said the study "provides strong evidence for brain capillary damage and BBB breakdown in hippocampus as early biomarkers of cognitive dysfunction in older adults."

Results independent of aging and unrelated to traditional vascular risk-factor burden strengthen the findings, she added.

"Importantly, the studies reported indicate that early capillary damage and BBB breakdown are independent of changes in Aβ or tau, markers of inflammation and markers of neurodegeneration," Galvan said.

"The etiology of this early brain microvascular damage, and its long-term impact, thus, remain to be defined," she said.

She added that future follow-up studies may reveal potential relationships between early microvascular injury and the pathogenesis of dementias including, but not limited to, AD.

Although not involved with the current research, Galvan was principal investigator of a study suggesting that mTOR protects the BBB in experimental models of AD and vascular cognitive impairment.

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