Research provides strong link between delirium and inflammation in older patients

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Delirium is an acute state of confusion that often affects older adults following surgery or serious illness. Now a study led by researchers at Beth Israel Deaconess Medical Center (BIDMC) confirms that inflammation - an immune response that develops when the body attempts to protect itself from harmful stimuli—plays a role in the onset of delirium.

Published in *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, the new study found that older patients with delirium had significantly elevated levels of the inflammatory marker interleukin-6 (IL-6) two days after surgery and also identified elevated levels of interleukin 2 (IL-2) in delirious patients. Together, these findings may help clinicians identify patients at greatest risk of developing delirium and aid in the treatment of this condition, which occurs in up to 64 percent of hospitalized seniors and is associated with a two- to three-fold increase in the subsequent development of dementia.

"Delirium complicates hospital stays for millions of elderly individuals in the United States each year," said co-senior author Edward Marcantonio, MD, Director of the Aging Research Program in the Division of General Medicine and Primary Care at BIDMC and Professor of Medicine at Harvard Medical School (HMS). "With strong evidence for the involvement of IL-6 and evidence for the involvement of IL-2 in patients with delirium, it appears that inflammation is indeed a basic mechanism underlying this condition."

Anything that causes tissue injury - including infection or illness as well as surgery—can activate various immune cells and cause inflammation. "Delirium may be an inflammatory response gone awry," said Marcantonio.

In this new work, BIDMC researchers and co-lead authors Sarinnapha M. Vasunilashorn, PhD, and Long Ngo, PhD, examined data from a patient cohort called SAGES (Successful Aging after Elective Surgery Study). This large study sponsored by the National Institute on Aging has been following 566 noncardiac surgical patients over the age of 70 for the past five years with the goal of finding new approaches to prevent delirium and its long-term consequences in older adults.

"In examining SAGES patients who had undergone major elective

surgery, we compared patients who developed delirium with those who did not," explained Vasunilashorn, a postdoctoral fellow in the Division of General Medicine and Primary Care at BIDMC and HMS. Surgery types included orthopedic, vascular and gastrointestinal procedures.

After adjusting for a number of factors - including age, gender, surgery type, baseline cognition, presence of a vascular comorbidity and the presence of a genetic variant that has been associated with an increased risk of Alzheimer's disease - the authors used a three-stage approach to examine the association between inflammatory cytokines and delirium.

They first created what they called a discovery cohort from a dataset of the first 272 SAGES participants, in which the matching procedure identified 39 matched pairs of delirium cases and no-delirium controls. Second, they considered the remaining SAGES study sample to identify 36 matched pairs of cases and controls, called the replication cohort. Third, they combined these two cohorts to create the pooled cohort, which contained 75 matched pairs.

The researchers measured cytokines in blood samples taken prior to surgery to establish a baseline figure. Additional measurements were then taken at three separate time points. "We looked at cytokine measurements taken immediately following surgery in the post anesthesia care unit, then again two days following surgery while the patient was still in the hospital, and finally, one month post-surgery," said Vasunilashorn.

The researchers used a commercially available kit to assess 12 different inflammatory markers.

"Previous studies had used an older method to analyze patients' inflammatory markers," explained co-senior author George Kuchel, MD, a geriatrician at the University of Connecticut Health Center. "But this

method can measure only one cytokine at a time. Inflammation is a complicated phenomenon, and we wanted a complete picture of what was taking place. We needed to simultaneously measure multiple cytokines in order to evaluate networks of inflammatory pathways." Kuchel and his colleagues adapted and optimized a customized technique using a commercially available system to measure multiple cytokines from the same sample.

"The results showed that levels of IL-6 were significantly elevated in the delirium patients two days after surgery, said Vasunilashorn. "The magnitude of difference in levels of IL-6 between delirious and non-delirious patients was about 10 times the upper limit for normal levels in older adults."

Moderate evidence for IL-2 was also reported: In the pooled cohort, delirious patients had higher levels of IL-2 at all four time points relative to non-delirious patients. "The role of IL-2 in delirium is a new finding and is particularly interesting since it was reported to induce blood-brain barrier dysfunction in animal models," she added.

"Although we found IL-6 elevated significantly in the delirious patients two days after surgery, we did not find the elevation to be statistically significant at one month following surgery," said co-lead author Ngo, biostatistician in the Division of General Medicine and Primary Care at BIDMC and Associate Professor of Medicine at HMS. "Does the duration of the elevation relate to delirium severity or delirium persistence? This is a question we have yet to answer. However, by identifying a strong IL-6 signal, we have a good opportunity to study how this potential biomarker fits into the causal pathway of delirium."

Most prior research on inflammation and delirium has collected information at a single point in time. "Given the dynamic nature of the inflammatory response, our collection of blood at four separate points

gives us a more complete picture," explained Vasunilashorn. Additionally, because the first blood samples were collected preoperatively in patients undergoing scheduled major surgery, the measures represent a true baseline condition. "Previous studies examined patients undergoing hip-fracture repair or other urgent surgeries, in which initial blood samples were collected after a significant stressor had already occurred," she added.

"Delirium is the most common complication among hospitalized elders," says Marcantonio. "Once widely assumed to be a short-term, transient condition, there is now evidence that delirium and its effects can last long after patients have left the hospital. We want our patients to get better, not worse, after a hospitalization. Understanding the role that inflammation plays in the onset of delirium can help us identify patients who may be at highest risk of developing this condition, and take steps to reduce their risk. It can also help design new interventions to prevent or treat delirium."

Provided by Beth Israel Deaconess Medical Center