

# Strong Link Seen Between Depression, Inflammation

BY DAMIAN McNAMARA  
Miami Bureau

SAN JUAN, P.R. — Growing evidence points to an association between inflammation and depression, according to a presentation at the annual meeting of the American College of Psychiatrists.

For example, depressed patients have elevated inflammatory markers—such as interleukin-6 and C-reactive protein. In fact, the levels of proinflammatory cytokines correlate with the severity of depressive symptoms in studies. In addition, administration of cytokine antagonists can effectively reverse depressive symptoms in patients, Dr. Andrew H. Miller said.

“We really stand at a point that is very exciting in terms of novel therapies and translation of research,” Dr. Miller said. “The notion quite simply is that stress or depression affects the HPA [hypothalamic-pituitary-adrenal] axis, [affects] the endocrine system, alters the immune system, and leaves patients open to diseases.”

Physicians from many specialties already recognize that inflammation plays a key role in cardiovascular disease, dia-

betes, metabolic syndrome, and cancer, said Dr. Miller, professor in the department of psychiatry and behavioral sciences at Emory University, Atlanta.

“We did not want to be left out in terms of psychiatry,” said Dr. Miller, who also is director of the psychiatric oncology program at the Winship Cancer Institute at Emory.

There are multiple possible mechanisms whereby inflammation could cause depression. Inflammatory cytokines released peripherally might reach the brain through active transport, passage through leaky regions in the blood-brain barrier, or transmission through afferent nerve fibers (vagus nerve), Dr. Miller said. There is a cytokine network in the central nervous system, and glia and microglia are the richest source of cytokines in the brain. Neurons also produce and express cytokines.

“We’ve learned these cytokines have access to the brain and ... ultimately can change behavior,” Dr. Miller said. Inflammatory cytokines cause anhedonia, fatigue, cognitive dysfunction, and other flu-like symptoms in sick patients. In addition, researchers induced behavioral changes that resemble major depression in human and animal studies with administration of proinflammatory cytokines.

Some therapeutic cytokines cause depression. For example, interferon- $\alpha$  (IFN- $\alpha$ ) is used to treat viral infections

and cancer because it is a potent inducer of the inflammatory cytokine network, especially interleukin-6, Dr. Miller said. “Oncologists told us early on this drug causes a lot of depression.”

A total of 60% of patients treated with IFN- $\alpha$  reported depressed mood in one study (*Neuropsychopharmacology* 2002;26:643-52). Dr. Miller and his associates also found a 45% incidence of major depression among patients with malignant melanoma treated with IFN- $\alpha$  (*N. Engl. J. Med.* 2001;344:961-6).

The good news is that paroxetine (Paxil) aggressively blocked development of depression. “Just 11% developed depression, so there was a four-fold reduction with this pretreatment.

“There is a caveat. If you give a drug that causes release of dopamine—for

example, paroxetine—that dopamine becomes oxidized and in the long term can damage basal ganglia,” Dr. Miller said in response to a question from a person attending the meeting. “So we’re using dopamine antagonists to block this until we get more information about what we are doing to patients.”

Physician reaction to his study varied, Dr. Miller said. “The people

who got on us the most for that study with paroxetine were the ones who were treating hepatitis C. They said we’d expose a lot of people to antidepressants who don’t really need them.” However, “with melanoma, many patients will not go back on interferon therapy, and giving antidepressant prophylaxis might help.”

In another study, patients with psoriasis treated with the cytokine antagonist etanercept experienced reversal of their depressive symptoms (*Lancet* 2006;367:29-35). Improvement in depression was independent of the drug’s effect on disease progress.

The wider picture may be a link between stress, depression, and illness, Dr. Miller said. In one study in review, patients with major depressive disorder exhibited an exaggerated inflammatory response to stress.

“There is an interesting possible link between depression and a wide variety of medical disorders where inflammation plays a role,” Dr. Miller said. It “may explain high comorbidity of some medical conditions with depression.

“Psychiatry is now catching up to other medical specialties in recognizing the adverse effects of inflammation,” Dr. Miller added. “Psychiatrists need to keep an eye on this. The idea that the immune system might affect the brain and vice versa presents a lot of novel targets for treating psychiatric disorders.” ■

# Postop Neurocognitive Dip Tied To High Inflammatory Markers

BY DOUG BRUNK  
San Diego Bureau

SAN DIEGO — Increased levels of C-reactive protein and other markers of perioperative inflammatory response are associated with neurocognitive decline following cardiac surgery, Dr. Basel Ramlawi said at a congress sponsored by the Association for Academic Surgery and the Society of University Surgeons.

Dr. Ramlawi and his associates prospectively evaluated 41 patients who underwent coronary artery bypass graft and/or valve procedures that used cardiopulmonary bypass. The patients’ mean age was 67 years. All patients had neurocognitive testing preoperatively, postoperatively at day 4, and at 3 months. The validated tests took 45 minutes to administer and covered memory, executive function, naming, attention, fluency, and premonitory intelligence, said Dr. Ramlawi of the division of cardiothoracic surgery at Harvard Medical School, Boston. Neurocognitive decline was defined as performing one standard deviation from baseline on at least 25% of tasks.

Participants also underwent serum testing preoperatively, postoperatively at 6 hours, and at 4 days. Levels of C-reactive protein (CRP) and of interleukin 1 $\beta$ , IL-6, and IL-10 were assessed, and an increase of serum tau protein after surgery was used as a marker of axonal central nervous system damage.

Of the 41 patients, 7 (17%) developed neurocognitive decline. Baseline characteristics and predictors of neurocognitive decline such as age, education level, and peri-

operative temperature did not differ significantly between patients with and without postoperative neurocognitive decline.

However, patients who experienced postoperative neurocognitive decline had significantly greater increases of CRP, IL-1 $\beta$ , and IL-10 than those who had no decline.

In addition, the level of tau protein was increased 78% in patients with neurocognitive decline, compared with 29% in their counterparts who did not show a decline.

“There exists a significant association [between] the magnitude and persistence of the perioperative inflammatory response and neurocognitive decline in this cohort,” Dr. Ramlawi said. “This association is likely mediated by axonal damage.”

According to the medical literature, the incidence of neurocognitive decline is 20%-60% in the first 2 weeks after cardiac surgery. “It can range from 5% to 40% for periods up to 5 years after surgery,” he said, adding that the etiology of this complication is not known.

“It is likely a multifactorial problem,” Dr. Ramlawi said. “Several theories have been assessed. The most obvious one is ischemia. Any microemboli might cause this.”

Other possible factors include anesthesia, perioperative hypothermia, and low level of education.

“While there have been certain markers of brain injury following cardiopulmonary bypass, very few have been associated with clinical outcomes and neurocognitive decline,” he said. “Tau protein, on the other hand, assesses axonal damage and has not been [studied] in cardiac surgery before.” ■

# Rape Associated With Increases in Headaches, Pain, GI Disorders

SAN FRANCISCO — Rape appears to initiate a host of neuroinflammatory changes that could predispose the victim to later inflammatory disease, Maureen Groer, Ph.D., said at the annual meeting of the Society of Behavioral Medicine.

“Victims of rape experience more headaches, chronic pain, gastrointestinal disorders, breast cancer, and arthritis—many of which have an inflammatory component,” said Dr. Groer, a registered nurse at the University of South Florida, Tampa. “About a third of them also develop posttraumatic stress disorder, which is also associated with an increase in inflammatory disorders.

“I would suggest that this could be explained by psychoneuroimmunology, in which stressors appear to provoke an immune response that can lead to damage of normal tissues if it is prolonged.”

To examine the relationship between rape and inflammatory response, Dr. Groer compared lymphocyte counts and cytokine and hormone levels in a group of 16 healthy control women who had low self-reported stress with those in a group of 15 victims of recent, first-time rape. Blood was collected from the rape victims within 72 hours of their assault (most within 24 hours). The rape victims’ mean age was 30 years; that

of the control group was 24 years. None of the women were living in domestic abuse or violent situations.

Serum analysis revealed that levels of CD8 cytotoxic cells were significantly higher in rape victims than in controls (10% vs. 6%), and CD19 percentages were significantly lower in rape victims compared with controls (6% vs. 20%).

Compared with controls, rape victims also expressed much higher levels of interferon- $\gamma$  (10 times higher), interleukin-10 (four times higher), interleukin-6 (five times higher), and C-reactive protein (three times higher). These data suggest an acute inflammatory process.

Nurses who examined the rape victims also noted victims’ behavior as controlled (quiet and withdrawn) or uncontrolled (angry or lashing out). Most of the victims were controlled; control correlated with lower CD4 counts, reduced CD4/CD8 ratios, and lower lymphocyte proliferation. “This suggests a state of T-cell suppression,” Dr. Groer said. “The inflammatory response system may dominate and deplete the adaptive resources of the women, and provoke a pathophysiologic state leading to multiple adverse health outcomes.”

—Michele G. Sullivan