Markers of inflammation in the blood linked to aggressive behaviors

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People with intermittent explosive disorder—a psychiatric illness characterized by impulsivity, hostility and recurrent aggressive outbursts—have elevated levels of two markers of systemic inflammation in their blood, according to a study involving nearly 200 subjects.

The paper, published in the December 18, 2013, issue of *JAMA Psychiatry*, is the first carefully controlled study to document a direct relationship between inflammatory markers and recurrent, problematic, impulsive aggression in people diagnosed with intermittent explosive disorder, but not in people in good mental health or those with other psychiatric disorders.

"These two markers consistently correlate with aggression and impulsivity but not with other psychiatric problems," said senior study author Emil Coccaro, MD, the Ellen C. Manning professor and chairman of the Department of Psychiatry and Behavioral Neuroscience at the University of Chicago. "We don't yet know if the inflammation triggers aggression or aggressive feelings set off inflammation, but it's a powerful indication that the two are biologically connected, and a damaging combination."

Intermittent explosive disorder (IED), a disorder of impulsive aggression (which includes "road rage"), can disrupt the lives of those with the disorder, as well as the lives of their family, friends and colleagues. People with IED overreact to stressful situations, often with uncontrollable anger and rage.

IED outbursts are out of proportion to the social stressors triggering them. Such blow-ups may at first be written off by friends as "simple bad behavior," Coccaro said, "but intermittent explosive disorder goes beyond that. It has strong genetic and biomedical underpinnings. This is a serious mental health condition that can and should be treated."

In addition to professional and social problems, IED can predispose people to other mental illnesses, including depression, anxiety, and alcohol or drug-abuse. Those with IED face increased risk for non-behavioral health issues, including coronary heart disease, hypertension, stroke, diabetes, arthritis, ulcers, headaches and chronic pain, according to a 2010 study.

IED is common. In 2006 Coccaro and colleagues at Harvard Medical School found that the disorder affects up to 5 percent of adults, or about 16 million Americans, in their lifetimes. Typically, the first episode of rage occurs in adolescence, around age 13 for males and age 19 for females.

In the *JAMA Psychiatry* study, the researchers focused on blood levels of two markers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6), each of which has been associated with impulsive aggressive behaviors in humans, cats and mice.

CRP is produced by the liver in response to an infection or injury. It helps focus the immune system's attention on dead or damaged cells. IL6 is secreted by white blood cells to stimulate immune responses, such as fever and inflammation. It also increases production of CRP.

The researchers measured CRP and IL6 levels in 197 physically healthy volunteer subjects. Sixty-nine of those subjects had been diagnosed with IED, 61 had been diagnosed with psychiatric disorders not involving aggression, and 67 had no psychiatric disorder.

Both CRP and IL-6 levels were higher, on average, in subjects with IED, compared to either psychiatric or normal controls. Average CRP levels, for example, were twice as high for those with IED as for normal healthy volunteers. Both markers were particularly elevated in subjects who had the most extensive histories of aggressive behaviors. Each

marker independently correlated with aggression, the authors note, suggesting that "both have unique relations with aggression."

Earlier studies have pointed to connections between an inflammatory response and depression or stress, said Coccaro. Healthy people who have been exposed to endotoxins—which set off a powerful immune reaction—have a much more robust brain reaction to exposure to social threat, such as photographs of an angry or fearful face, than those who were not exposed to endotoxin.

Overall, the findings reported in this new paper suggest that "medications that reduce inflammation may also drive down aggression," Coccaro said. Anti-inflammatories such as Celebrex, or even aspirin, might make a difference for those with IED. Since available treatments bring less than 50 percent of patients into remission, the authors wrote, "additional strategies for the examination and intervention of human impulsive aggression are needed."

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