Researchers find evidence of DNA damage in veterans with Gulf War illness

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Yang Chen, with the War Related Illness and Injury Study Center at the Veterans Affairs New Jersey Health Care System, was first author on a study that found mitochondrial DNA damage in veterans with Gulf War illness. Credit: Mitch Mirkin

Researchers say they have found the "first direct biological evidence" of

damage in veterans with Gulf War illness to DNA within cellular structures that produce energy in the body.

The findings appeared in the journal *PLOS One* in September 2017.

A study that focused on mitochondrial DNA (mtDNA) included 21 veterans with Gulf War illness (GWI) and seven controls.

In blood tests, researchers observed more lesions and more mitochondrial DNA—that is, extra copies of genes—in veterans with Gulf War illness, relative to controls without the illness, suggesting excess DNA damage. Lesion frequency gives a direct measure of DNA damage, while the increased number of mtDNA copies reflects a response to the damage.

Both lesion frequency and the number of mtDNA copies vary in response to environmental toxins and together provide a reading of overall mitochondrial health, according to lead researcher Dr. Mike Falvo, a health sciences specialist at the Veterans Affairs New Jersey Health Care System.

He notes that everyone experiences some level of mtDNA damage, perhaps due to aging and environmental exposures, such as air pollution. In the study, the mtDNA damage was 20 percent greater in the veteran group, compared with a control group that included three veterans without GWI and four non-veterans.

"Greater mtDNA damage is consistent with mitochondrial dysfunction, which may contribute to symptoms of GWI, as well as persistence of this illness over time," the researchers write. "We interpret these findings as evidence that mitochondrial dysfunction is involved in the pathobiology of GWI."

Falvo explains that the researchers used a new technique developed in the lab of his team's collaborator that allowed them to evaluate the quality of the mitochondrial DNA directly from total DNA without having to isolate the mitochondria. This approach is simpler to execute and does not require analysis through a biopsy of a piece of tissue, such as skeletal muscle, he says.

Although Falvo and his team were interested mainly in mtDNA, they also looked at nuclear DNA, which is vital, too, to overall mitochondrial health. The levels of nuclear DNA damage were also elevated in the veterans with GWI, but did not reach "statistical significance," the researchers say. Nuclear DNA damage is a major cause of cancer, neurodegeneration, mitochondrial dysfunction, and many age-related diseases.

Mitochondria are organs that act as spark plugs within cells. They are like a digestive system that takes in nutrients, breaks them down, and creates energy-rich molecules for the cell. They are very sensitive to potential damage caused by toxins.

Patients with mitochondrial dysfunction have symptoms involving multiple organ systems, primarily nerves and muscles. Veterans with Gulf War illness have reported similar symptoms. Many Gulf War veterans believe they were exposed to harmful chemicals and other toxins during the conflict.

"Mitochondrial dysfunction among veterans with GWI may help explain, in part, the persistence of this illness for over 25 years," the researchers on Falvo's study write. "For example, chemical and environmental exposures during deployment may have provided the initial [harm] to mtDNA and accumulation of damage."

Falvo, also an assistant professor at Rutgers New Jersey Medical School,

researches how cardiovascular, cardiorespiratory, and other systems respond to physical and environmental stress.

Soon after joining VA in 2010, he learned that many Gulf War veterans experience major fatigue and other symptoms across many areas of the body. "To me, that sounded awfully consistent with the symptoms of mitochondrial disorders," he says. "After reviewing the literature, I realized at that time there was no published study on GWI that investigated whether mitochondrial dysfunction contributed to symptoms."

He explored that potential link with Dr. Helene Hill, a colleague at Rutgers New Jersey Medical School who has studied mitochondrial DNA. Their discussion led to preliminary data that supported Falvo's 2017 study, on which Hill is a co-investigator.

Falvo's study follows work by Dr. Beatrice Golomb at the University of California, San Diego. Golomb was formerly on VA's Research Advisory Committee on Gulf War Veterans' Illnesses. With Department of Defense funding, she and her team reported in 2014 what they called "the first direct evidence supporting mitochondrial dysfunction in Gulf War illness."

Falvo and his colleagues performed tests directly on the mitochondrial genome. In contrast, Golomb used an imaging technique to examine the oxidative capacity of muscle in veterans with Gulf War illness. Oxidative capacity of muscle is a measure of how well tissue, or muscle, is able to use oxygen. In essence, the more mitochondria that are functioning well, the more that tissue is able to use oxygen.

The researchers in Golomb's study called, in part, for replication of their findings in a larger study. Falvo's research includes three times the number of veterans with Gulf War illness.

In a separate 2014 study of 46 veterans with GWI, Golomb and her colleagues reported promising results for the nutritional supplement coenzyme Q10 (CoQ10) as a way to address the fatigue created by mitochondrial dysfunction. CoQ10 is thought to promote healthy mitochondria.

VA recently launched a three-year trial to determine if treatment with ubiquinol, a form of CoQ10, improves the physical function of veterans suffering from Gulf War illness.

The study is being carried out at four VA medical centers: Miami, Boston, Minneapolis, and the Bronx, New York. Officials there are recruiting 200 veterans with GWI for a double-blind placebo study. The initiative is based on data supporting the need for methods that repair mitochondrial function and that replenish depleted antioxidant stores related to the illness, according to the principal investigator, Dr. Nancy Grace Klimas of the Miami VA Healthcare System.

Antioxidants are substances, such as vitamin C or beta carotene, that remove potentially damaging oxidizing agents in a living organism.

In a sister study, Dr. Mary Ann Fletcher of the South Florida Veterans Affairs Foundation for Research and Education, a nonprofit group that supports VA research, is exploring changes in biomarkers related to CoQ10 treatment. These biomarkers include inflammatory cytokines, which are substances that are secreted by certain cells in the immune system and impact other cells; and natural killer (NK) cells, which play a major role in the hosting and rejection of tumors and virally infected cells.

Falvo, for his part, is expanding his team's efforts to study mitochondrial DNA damage in veterans with Gulf War illness. He's part of a new DoD-supported study led by Dr. Joel Meyer, an associate professor at Duke

University in Durham who studies environmental toxicology. The researchers are seeking to recruit about 150 veterans with and without GWI in hopes of confirming the findings in Falvo's 2017 study. "More importantly, we want to gain new knowledge of the damage of mtDNA on mitochondrial function and the recovery process," he says.

"We need to be sure that our findings are robust," Falvo says. "For us, that means confirming the present results but also investigating what might be contributing to mitochondrial DNA damage or its lack of repair."

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