



Insight Into Mechanisms of ME/CFS

Researchers saw important differences in people with post-infection myalgic encephalomyelitis/chronic fatigue syndrome.

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) involves debilitating fatigue, intolerance to exercise, and cognitive problems. Symptoms tend to get worse after even mild exertion. The cause remains unknown, hampering development of treatments. ME/CFS often develops after an infection—a condition known as post-infectious-ME/CFS (PI-ME/CFS).

A research team led by NIH's Dr. Avindra Nath conducted an in-depth study of 17 people with PI-ME/CFS and 21 healthy volunteers. Their aim was to uncover key features that might be driving PI-ME/CFS. Results [appeared in Nature Communications](#) on February 21, 2024.

People with PI-ME/CFS had higher heart rates throughout the day and a smaller drop in their nighttime heart rate than healthy volunteers. This suggests that the autonomic nervous system, which controls unconscious bodily functions, is disrupted in PI-ME/CFS. Heart and lung function were also less able to respond to exercise in people with PI-ME/CFS.

In one test, participants were repeatedly given the choice of performing either an easy task for a low reward or a hard task for a higher reward. Those with PI-ME/CFS were less likely to choose the hard task than the healthy volunteers, suggesting less ability to exert effort. The healthy volunteers had reduced muscle function and brain motor cortex activity after repeated tasks. But people with PI-ME/CFS did not. Brain scans during one task found that those with PI-ME/CFS had lower activity in a brain region called the temporoparietal junction. These findings suggest that the fatigue of those with PI-ME/CFS might be caused by dysfunction in the way the brain decides how to exert effort.

When the team analyzed cerebrospinal fluid, they found that participants with PI-ME/CFS had reduced levels of chemicals called catechols. Catechols help regulate the nervous system. Catechol levels correlated with effort preference and motor function in people with PI-ME/CFS, but not in healthy volunteers. This suggests that altered catechol signaling in the brains of people with PI-ME/CFS may give rise to their altered effort.

The team examined immune function as well. They found differences in B cells, which make antibodies to help fight pathogens. People with PI-ME/CFS had more naïve B cells, which can be activated by any foreign substance. But they had fewer switched memory B cells, which respond

to a specific pathogen that the body has encountered before. B cell dysfunction was more prominent in women. These findings suggests that the immune system continues to be activated in the absence of infection.

Taken together, the results suggest that PI-ME/CFS may be caused by immune system dysfunction that is triggered by infections. This may lead to chemical changes in the central nervous system that affect certain brain functions to cause ME/CFS symptoms.

“Rather than physical exhaustion or a lack of motivation,” says first author Dr. Brian Walitt, “fatigue may arise from a mismatch between what someone thinks they can achieve and what their bodies perform.”

“Men and women were quite divergent in their data,” Nath notes, “and that tells you that ME/CFS is not one-size-fits-all. Considering male and female immune differences in ME/CFS, the results may open up new avenues of research that could provide insight into other infection-associated chronic diseases.”

The findings also suggest ways in which PI-ME/CFS might be treated, either by targeting the immune system or specific circuits in the brain.

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