Scientists discover biological evidence of 'atypical' chronic fatigue syndrome

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Scientists at the Center for Infection and Immunity (CII) at Columbia University's Mailman School of Public Health are the first to report immune signatures differentiating two subgroups of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): "classical" and "atypical." This complex, debilitating disease is characterized by symptoms ranging from extreme fatigue after exertion to difficulty concentrating, headaches, and muscle pain.

The study appears in the Nature Publishing Group journal, *Translational Psychiatry*.

Typically, symptoms of ME/CFS begin suddenly following a flu-like infection, but a subset of cases classified by the investigators as "atypical" follows a different disease course, either from triggers preceding symptoms by months or years, or accompanied by the later development of additional serious illnesses.

To uncover evidence of these disease types, first author Mady Hornig, MD, director of translational research at CII and associate professor of Epidemiology at Mailman, and colleagues used immunoassays to measure levels of 51 immune biomarkers in cerebrospinal fluid samples taken from 32 cases of classical and 27 cases of atypical ME/CFS. All study participants were diagnosed using the same standard criteria, but atypical cases either had prior histories of viral encephalitis, illness after foreign travel or blood transfusion, or later developed a concurrent malady—seizure disorders, multiple sclerosis-like demyelinating

disorders, Gulf War Illness, or a range of cancers—at rates much higher than seen in the general population.

Their analysis revealed lower levels of immune molecules in individuals with atypical ME/CFS than those with a classical presentation and course of illness, including dramatically lower levels of interleukin 7 (IL7), a protein linked to viral infections, and interleukin 17A (IL 17A) and chemokine (C-X-C motif) ligand 9 (CXCL9), inflammatory molecules implicated in a variety of neurological disorders.

"We now have biological evidence that the triggers for ME/CFS may involve distinct pathways to disease, or, in some cases, predispose individuals to the later development of serious comorbidities," says Hornig. "Importantly, our results suggest that these early biomarker profiles may be detectable soon after diagnosis of ME/CFS, laying a foundation for better understanding of and treatments for this complex and poorly understood illness."

"Early identification of patients who meet the usual clinical criteria when first diagnosed but then go on to develop atypical features would help clinicians like myself identify and treat these complex cases and even prevent fatal outcomes," says co-author Daniel L. Peterson, MD, principal clinician at Sierra Internal Medicine in Incline Village, NV.

Subgroups

The new study builds on earlier research by Hornig and collaborators that found robust evidence of distinct stages in ME/CFS. A pair of 2015 publications based on analyses of blood and cerebrospinal fluid showed differences in the immune signatures of ME/CFS patients who had the disease for three years or less as compared with those who had been ill for more than three years. The researchers reported that patients were flush with cytokines and chemokines until around the three-year

mark—suggesting an over-activated immune response in that phase of the illness; thereafter the immune system showed evidence of "exhaustion," and levels of immune molecules dropped.

In the new study, both subsets of ME/CFS patients showed signs of an unbalanced or dysregulated immune system within the central nervous system, with immune markers different than those seen in healthy individuals. However, the dampened immune profiles previously observed after the three-year mark were only observed in individuals with the classical form of the disease, not in those with atypical ME/CFS. Among subjects in the atypical group, levels of cytokines and chemokines were more likely to remain steady or increase.

According to Hornig, instead of the immune exhaustion seen in later phases of classical ME/CFS, atypical patients may be experiencing a "smoldering inflammatory process" in which the immune system is still working to recover, although she acknowledges that much work remains to be done to confirm this hypothesis. Alternatively, these findings could suggest a pathway to disease in atypical individuals that involves biomarkers not captured in the 51-molecule assay, potentially even involving non-immune-related processes. Atypical individuals may also have genetic susceptibilities that lead their immune systems to respond differently than in classical cases.

Ongoing studies at CII are exploring other subgroups, including patients with allergic disorders, high levels of cognitive dysfunction, and gastrointestinal disturbances.

"Multiple biological pathways are likely involved in the pathogenesis of ME/CFS, with a range of clinical subtypes relating to variability in the types of environmental triggers, genetic and epigenetic vulnerability, as well as comorbidity patterns," says senior author Ian Lipkin, MD, director of CII. "Shedding light on these pathways may help us to

identify the various agents that precipitate disease as well as to design more precise, targeted treatments."

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