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Chronic Fatigue Syndrome: Immune Alterations Seen Early

Miriam E. Tucker | March 02, 2015

Patients with recent-onset myalgic encephalomyelitis/chronic fatigue syndrome had distinct alterations in plasma immune signatures in an analysis of data and blood specimens from two large multicenter cohort studies.

The findings were published online February 27 in *Scientific Advances* by Mady Hornig, PhD, from the Center for Infection and Immunity and the Department of Epidemiology, Columbia University Mailman School of Public Health, New York City, and colleagues.

Patients who were within 3 years of developing the illness, which has now been renamed "systemic exertion intolerance disease" by the Institute of Medicine, had prominent activation of both proinflammatory and anti-inflammatory cytokines and dissociation of intercytokine regulatory networks, suggesting a potential biomarker for diagnosing the condition, the authors say.

"The presence of a specific immune profile early in the course of ME/CFS has important implications for the diagnostic process.... [W]e were able to define a distinctive immune signature that differed from that of healthy controls. Integration of these immune markers with clinical findings will provide clinicians with a stronger framework for establishing an ME/CFS diagnosis, and, possibly, make it easier to rule out other conditions at an earlier time point," Dr Hornig and colleagues write.

For reasons that are not clear, the findings in recent-onset patients contrasted both with those of controls and with those of patients with a longer illness duration.

According to Dr Hornig and colleagues, "the restriction of this pattern of immune disturbances to short-duration as opposed to long-duration cases suggests that both the dysregulation of immune cell interactions...and the opportunities for intervention may be transient. Therapeutic strategies that specifically target abnormalities found in these early immune profiles may present novel but time-limited opportunities not only for remediation but potentially also for staving off the long-term, chronic decline associated with ME/CFS."

William Schaffner, MD, professor of medicine at Vanderbilt University in Nashville, Tennessee, and a noted expert in infectious disease and vaccines, told *Medscape Medical News*, "This illness has been very difficult to define.... What I like about this paper is they're looking for light at the end of the tunnel. They're not starting etiologically, but defining the pathophysiology. And it does look as though in this one study, there's a biphasic phenomenon, earlier and later, with different immunologic criteria. It's interesting, provocative, and I think lends itself to a hypothesis which is at least consistent with clinical observations. So, it has the attractiveness of coherence. And, it's a study that's replicable."

Such replication, he said, should be conducted by other investigators who "have populations of patients [with] CFS with similar appropriately chosen controls and all the precision that has been done with study.... I think the findings are sufficiently robust and provocative and coherent that they ought to command funding, whether from private or public sources."

Distinct Pattern in Short-Duration Illness

The researchers studied clinical databases from two large multicenter cohort studies assessing the relationship of immune signatures, investigating a total of 51 inflammatory cytokines, with diagnosis and clinical variables One database was funded by the National Institute of Allergy and Infectious Diseases, and the other was from the philanthropically funded Chronic Fatigue Initiative.

Diagnostic criteria were stricter for the National Institutes of Health cohort, which required patients (aged 18 - 70 years) to meet both the 1994 Centers for Disease Control and Prevention's CFS criteria and the 2003 Canadian Consensus criteria for ME/CFS, and all had to have had a viral-like prodrome. With the Chronic Fatigue Initiative cohort (aged 18 - 65 years), subjects only had to meet one or the other definition.

In all, there were 52 adult patients with illness onset (not diagnosis) within 3 years, 246 with illness duration longer than 3 years, and 348 controls matched for age, sex, and variables known to affect immune status, including season of sampling and geographic site. Plasma samples were collected at the same time of day under controlled conditions of mild stress (completing study forms).

When all the cases were combined, there were few major differences in inflammatory cytokine levels between cases and controls.

However, the researchers found significant differences in more than half of the 51 cytokines when the patients with short-duration and longer-duration ME/CFS were compared individually with the controls (with and without adjustment for sex and age).

Overall, the short-duration patients had higher levels of both proinflammatory and anti-inflammatory cytokine levels compared with the controls, including the proinflammatory cytokines interleukin 1a (IL-1a; *P* = .0178), IL-8 (*P* = .0112), IL-12p40 (*P* = .0009), IL-17A (*P* = .0243), and TNF-α (*P* = .0261) and the anti-inflammatory cytokines IL-1RA (*P* = .0105), IL-4 (*P* = .0028), and IL-13 (*P* = .0198). Two of the 51 cytokines were reduced in the short-duration ME/CFS group compared with controls: CD40 ligand (*P* = .0037) and platelet-derived growth factor BB (*P* = .0004).

Patterns were similar when comparing the short-duration with the long-duration patient groups. With logistic regression modeling, two proinflammatory cytokines were notably elevated in the short-duration group compared with the longer-duration group: Interferon gamma (odds ratio, 104.77) and IL-12p40 (odds ratio, 1.501).

Dr Hornig and colleagues say this marked association with interferon gamma in the early phase of illness is consistent with a viral trigger or disrupted immune regulatory networks. Interferon gamma can disrupt immune cell homeostasis, resulting in greater vulnerability toward developing certain types of autoimmune responses.

Network diagrams of intercytokine correlations revealed another difference between the short-duration ME/CFS group and both the long-duration group and the controls: CD40 was not only reduced, but its action was related to only five other cytokines, whereas in the longer-duration and control groups, it drove most of the inverse relationships with other immune molecules.

The finding of both decreased and dissociated CD40 is "intriguing," the authors say, noting that although the transmembrane protein is essential for the regulation of B-cell maturation and other functions, abnormally high levels have been linked to adverse neurovascular events, mild cognitive impairment, and Alzheimer's disease.

Moreover, they add, constitutive CD40L deficiency is associated with both susceptibility to recurrent infections and neurocognitive decline that is unexplained by the presence of any known pathogen or clear signs of encephalitis.

Cytokine alterations were more closely correlated with illness duration than with global illness severity measures, "suggesting that the immunopathology of ME/CFS is not static," they write.

The reason for the lack of findings in the longer-duration group is not clear, but might represent an "exhaustion" phenomenon similar to that seen in pancreatic beta cell production in people with long-duration type 2 diabetes. "We can only speculate," Dr Hornig and colleagues remark.

Indeed, Dr Schaffner called the biphasic aspect of the data "intriguing and bothering" and said it needs to be investigated further.

He told *Medscape Medical News*, "Many of us have over the years hoped for an etiologic agent [for ME/CFS]. We still don't have one, but now we may have some insights into the pathophysiology. I'm optimistic, but I've been optimistic in the past so my optimism is guarded.... I wish these investigators well."

The study was funded by the Hutchins Family Foundation. Dr Schaffner serves on data safety monitoring boards

for experimental vaccines studies for Pfizer and Merck.

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