

Metabolic features of chronic fatigue syndrome revisited

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In a recent paper in PNAS by Naviaux et al. (1) on metabolomics in chronic fatigue syndrome (CFS), the authors claim to have discovered an objective, diagnostically useful “chemical signature” of the condition, and that this signature corresponds to a “hypometabolic response to environmental stress similar to dauer.” Although we salute the authors’ methodological efforts and interesting findings, we have serious concerns regarding their interpretation.

First, by stating that CFS has a chemical “signature,” the authors suggest that they have discovered something very specific. However, findings of metabolic differences between patients with CFS and healthy controls do not automatically yield a test that can single out a specific disease. The authors have not investigated the diagnostic specificity in relation to other conditions with a phenotype similar to CFS, such as fibromyalgia (2). They have also not explored metabolomics in otherwise healthy subjects who have been in a state of prolonged, profound inactivity and stress, or in other chronic conditions characterized by reduced bodily activity, such as cardiac failure. For all we know, a similar metabolic response might be present in all these conditions. Moreover, the clinical definitions of CFS are based on pragmatic agreements among researchers, and lack proper validation (3). Thus, the scientific reasoning comes close to a tautology. First, one defines a clinical syndrome and assumes that it represents a specific disease; then, one finds a correlate to one’s own construct and uses this correlate as “proof” of its specificity. The authors’ own statement that “comparison with related medical disorders like depression and posttraumatic stress disorder will be needed to validate the universality and specificity of these findings” (1) also makes it clear

that their discovery of a signature of CFS/myalgic encephalomyelitis is invalidated.

Second, when discussing the possibilities of novel therapeutics, the authors seem to assume that their findings of metabolic alterations in CFS suggest a causal explanation of patients’ clinical symptoms. Evidently, the cross-sectional nature of their design does not allow causal claims to be made. More generally, results obtained at the metabolic level do not automatically mean that a disease should be understood at that level or that “personal” or “psychosocial” causes can be ruled out. A metabolic correlate to a clinical syndrome does not explain why these abnormalities are there.

Third, their discussion of a dauer response to environmental stress involves two references that mostly concern the nematode *Caenorhabditis elegans* (4, 5). Although this reference may not be irrelevant, the authors missed the opportunity to contextualize their findings in relation to clinical CFS research and stress theories (6–8). In humans, stress responses necessarily involve orchestrated neuroendocrine signaling, which, in turn, is influenced by mental states, such as conscious and unconscious interpretation of the surroundings (8). Thus, the findings of a possible dauer response in CFS might add to the growing body of evidence suggesting that complex relationships between different levels of biological organization, from the behavior of the whole organism trying to adapt to a (social) environment, via organs and cells to genetic variants, are core characteristics of this syndrome (6).

New technologies and diagnostic strategies that enable increased understanding of the fatigued person are much needed. However, to avoid undue hype, false hopes, and body/mind pitfalls, results should be interpreted with caution.

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