LETTER

# Metabolome of chronic fatigue syndrome

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Naviaux et al. (1) report on a distinct metabolic signature present in patients who have myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) compared with healthy controls. Metabolic pathway analysis is a growing field of interest, and could offer relevant pathophysiological or diagnostic clues in complex illnesses such as CFS. However, reviewing the patient selection and statistical methods used, we have some concerns.

First, the largest difference in metabolites was caused by a decrease of plasma sphingo- and glycosphingolipids in patients who had CFS. Sphingolipids have a broad range of action, and, currently, it is not completely clear which external factors can influence plasma concentrations. However, we do know that physical activity and exercise play a role and, for example, can lead to an increase in sphingoid base-1 phosphates (2). This knowledge could be relevant in the current patient category because patients with CFS usually are less physically active than healthy controls (3), which is also reflected, to some extent, by the lower Karnofsky score in patients. Unfortunately, physical activity was not measured in the current study, and controls were not selected based on their activity levels. Therefore, the difference in metabolic signature is likely to be at least partially due to differences in physical activity, as opposed to being a patient with ME/CFS or not. Furthermore, it would be interesting to have additional information on lifestyle factors such as diet and use of medication. Patients who have CFS often use antidepressants and different groups of over-the-counter drugs, which could be influencing plasma metabolites (4, 5).

Second, we have concerns regarding the statistical methods used. To start, the number of metabolites measured in this study is extremely high ($n = 612$) compared with the number of included individuals ($n = 84$). To generate a diagnostic model, the authors first use a nondescribed method to select 60 variables with a large discriminative value. Next, groups of five to 15 metabolites were selected and entered as candidate diagnostic classifiers. The performance of this model was tested on the same dataset that was used to design it, and yielded an area under the curve of 94% for males and 96% for females. This method is by no means reliable. Using this approach, selecting 60 of 612 predictors guarantees a very high level of apparent predictive performance, even if all predictors were just random variables. The set of metabolites should be tested in an independent cohort or at least be corrected for optimism that covers the entire selection of predictors, from the original 612 to the final set using internal validation methods. Only then proper insight into its diagnostic value for predicting CFS can be obtained.


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