Comment on “Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome”

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Lombardi et al. (Reports, 23 October 2009, p. 585) reported an association between the human gammaretrovirus XMRV and chronic fatigue syndrome. However, their results may be misleading because of various potential sources of bias and confounding. If real, the association may lack generalizability because of the specific characteristics of the cases studied and could be due to reverse causality.

Well-conducted case-control studies provide important insights into disease pathogenesis. Lombardi et al. (1) demonstrated an apparent association between chronic fatigue syndrome (CFS) and the presence, infectivity of, and immune response to the human gammaretrovirus, xenotropic murine leukemia virus–related virus (XMRV). However, their report has few features of a well-conducted case-control study, making their findings potentially misleading. Here, we briefly discuss several issues of study design, analysis, and interpretation, which may have contributed to inappropriate conclusions.

First, although the CFS cases studied fulfilled broadly accepted diagnostic criteria, they were selected from regions of CFS “outbreaks” and had specific immunological abnormalities, making them potentially more susceptible to viral infections than most patients with CFS. This could limit the generalizability of the study’s results. Second, to avoid selection bias, the CFS-free controls should have been drawn from the same background population as the cases and selected independent of the exposure (in this case, a viral infection) under study (2, 3). Put simply, the controls should ideally have been people who would have been cases in the study if they had CFS. However, the control subjects are not described in (1) beyond a mention that they were healthy donors. Third, the lack of clinical data for cases and controls makes it impossible to assess the potential for confounding by numerous other characteristics that may independently influence XMRV status, including age, sex, social deprivation status, medical history (e.g., of prostate cancer), and area of residence. Although confounding by demographic and clinical characteristics alone is unlikely to account for all of the observed difference in XMRV status between cases and controls, it could certainly be a contributory factor.

Fourth, Lombardi et al. do not explain whether identical and contemporaneous laboratory sample storage, handling, and analysis procedures were used for both cases and controls. Differences in these could be another potentially important source of confounding. Fifth, even if identical laboratory procedures for cases and controls were intended, researchers exploring an exciting new hypothesis of a viral cause for CFS in a laboratory established to explore biological causes of CFS will be understandably eager for positive results. This so-called “expectation bias” may lead to completely unconscious and nondeliberate differences in sample handling and data interpretation between cases and controls; it can be avoided only if researchers are blinded to the case-control status of the samples. However, this is not described in (1).

Finally, the criteria for selecting samples for further analyses (including XMRV protein expression in 30/101 cases and 16/218 controls, infectivity in 12 cases and 12 controls, and immune response in 18 cases and 7 controls) are not described and are another important source of potential bias. Was this selection made at random or without knowledge of case-control status? Were all case and control samples on which testing was performed included in data analyses?

Aside from these crucial methodological issues, other plausible alternative explanations for the findings are not explicitly discussed. Foremost among these is reverse causality: Patients with poor general health because of CFS may be more susceptible to viral and other infections. We welcome biological research in CFS but are concerned that Lombardi et al. (1) have not discussed the possibilities of bias, confounding, reverse causality, and lack of generalizability in their study. Patients with CFS, understandably desperate for answers, deserve high-quality research into their condition. Full details of the methodological issues described above should be published, so that the scientific community can properly assess the credibility of these findings. This is particularly important because three studies (including a total of 388 patients with CFS and 438 controls from the United Kingdom and the Netherlands) have now failed to demonstrate any link between XMRV and CFS (4–6).

References and Notes
5. H. C. Groom et al., Retrovirology 7, 10 (2010).

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