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 detection of the human gammaretrovirus XMRV in the blood cells of patients with chronic fatigue syndrome (CFS). However, the patient description provided was incomplete. The inclusion of patients from a "CFS outbreak" previously linked with a viral infection, without confirmation in sporadic CFS cases, casts doubt on the role of XMRV in the pathogenesis of CFS.

Chronic fatigue syndrome (CFS), a prolonged state of disabling physical and mental fatigue, has been linked often to an infectious etiology, with viruses such as Epstein-Barr virus, other herpesviruses, parvovirus B19 or enteroviruses, and bacteria such as *Coxiella burnetti* or *Mycoplasma species* being linked to the disease at one point or another (*1*). However, none of these associations have been confirmed in subsequent investigations, leaving the field and the patients in a continued state of uncertainty. At first glance, the recent study by Lombardi *et al*. describing the occurrence of the retrovirus xenotropic murine leukemia virus–related virus (XMRV) in 67% of patients with CFS would seem to be a scientific breakthrough (*2*), as this would pinpoint a clear etiology and pathogenesis, with important implications for prevention and treatment. Strikingly, this study also reported a prevalence of 3.7% of this virus in healthy Americans, with unknown and possibly far-reaching public health implications.

Surprisingly, the study by Lombardi *et al*. (*2*) falls short in the description of the patients: What was the nature of the cohort, the age and gender distribution of the patients, and the duration of illness? Did the patients fulfill the criteria of the Centers for Disease Control and Prevention? Moreover, it was surprising to learn during the presentation of this study at the 2009 Tri-Society Annual Conference in Lisbon (*3*) that the material studied was derived from patients from the well-publicized "outbreak" of CFS from Incline Village, Nevada, dating back to the 1980s. This outbreak has long been suggested to be caused by a viral infection, most notably with Epstein-Barr virus (*4*) or human herpes virus 6 (*5*). As a consequence, it is surprising that no independent cohort of patients with sporadic CFS was investigated by Lombardi *et al*., as these CFS cases represent the majority of patients. Investigation of such an independent cohort is necessary before a claim regarding the presence of the XMRV retrovirus in CFS patients is justified. This assessment has been provided by three recent independent studies (*6*–*8*). Erlwein *et al*. (*6*) failed to detect XMRV in any of the patients investigated from a cohort of well-characterized CFS patients from the United Kingdom, thus raising doubt about the role of XMRV in CFS. In addition, Groom *et al*. (*7*) failed to find any support for XMRV presence in another cohort of CFS patients from the United Kingdom, assessed by both polymerase chain reaction (PCR) and serological tests, and van Kuppeveld *et al*. (*8*) failed to detect XMRV by two different PCR methodologies in a cohort of Dutch patients.

In their detailed presentation of the immunological abnormalities in the patients, Mikovits also reported a cytokine profile with high interleukin-8 and macrophage inflammatory protein–1α and a low interferon-α concentration (*3*). The authors suggested that the selection of their group of CFS patients was partly based on reproducible immunological abnormalities and presented it as an additional argument for the viral etiology of CFS. Although this cytokine profile may be associated with a possible viral infection (while by no means being necessarily specific), it has not been reported previously as such in patients with CFS. The cytokine abnormalities in CFS patients are notoriously inconsistent (*9*), with some studies reporting increased (*10*), not different (*11*), or even lower (*12*) cytokine responses. Thus it is not possible to use "immunological abnormalities" as a selection criterion.

Therefore, we cannot but conclude that although the study of Lombardi *et al*. unravels the cause of an outbreak of viral infection, the etiology of sporadic CFS that represents the vast majority of patients remains uncertain. A note of caution should also be added regarding the putative geographic distribution of XMRV. XMRV was initially identified in prostate cancer patients in the United States (*13*), and this association was confirmed in a recent independent study from the United States (*14*). Remarkably, in three independent European cohorts of patients with prostate cancer, no XMRV was detected (*15*–*17*). Along the same lines, it would be of interest to see studies of XMRV in sporadic cases of CFS patients in the United States and elsewhere.

Over the past few decades, we have witnessed a long series of papers claiming the discovery of the cause of CFS. None of these claims has been confirmed. Each time, this gives false hopes to large numbers of patients who seek a solution for their suffering. Shortcomings in the study by Lombardi *et al*. now raise concerns about the role of XMRV in the pathogenesis of CFS.

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References and Notes

1. L. D. Devanur, J. R. Kerr, *J. Clin. Virol.* **37**, 139 (2006).
2. V. C. Lombardi *et al*., *Science* **326**, 585 (2009).
3. J. A. Mikovits, presentation at Conference on Cellular and Cytokine Interactions in Health and Disease, Lisbon, Portugal, 17 to 21 October 2009.
4. G. P. Holmes *et al*., *JAMA* **257**, 2297 (1987).
5. S. A. Daugherty *et al*., *Rev. Infect. Dis.* **13** (suppl. 1), S39 (1991).
6. O. Erlwein *et al*., *PLoS ONE* **5**, e8519 (2010).
7. H. C. Groom *et al*., *Retrovirology* **7**, 10 (2010).
8. F. J. M. van Kuppeveld *et al*., *BMJ* **340**, c1018 (2010).
9. M. Lyall *et al*., *J. Pysochosom. Res.* **55**, 79 (2003).
10. M. A. Fletcher, X. R. Zeng, Z. Barnes, S. Levis, N. G. Klimas, *J. Transl. Med.* **7**, 96 (2009).
11. C. M. Swanink *et al*., *J. Infect. Dis.* **173**, 460 (1996).
12. Y. Jammes, J. G. Steinberg, S. Delliaux, F. Brégeon, *J. Intern. Med.* **266**, 196 (2009).
13. A. Urisman *et al*., *PLoS Pathog.* **2**, e25 (2006).
14. R. Schlaberg, D. J. Choe, K. R. Brown, H. M. Thaker, I. R. Singh, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 16351 (2009).
15. N. Fischer *et al*., *J. Clin. Virol.* **43**, 277 (2008).
16. O. Hohn *et al*., *Retrovirology* **6**, 92 (2009).
17. F. D'Arcy *et al*., *Eur. Urol.* **7** (suppl.), 271 (2008).
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