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Gender Differences in Inflammatory Processes Could Explain Poorer Prognosis for Males

In their recent paper on the resurgence in mumps virus infections in Ireland (2), Carr et al. observed a strong ($P < 10^{-32}$) bias for acute mumps virus infection in males compared to females that was independent of vaccination status. The authors extrapolated to natural infections the gender differences in immune function observed in *in vitro* studies of human lymphoid cells and gender-based differences in humoral immunity with several vaccines, including those for influenza, hepatitis A, and measles virus. In another work on predicting sequelae and death after bacterial meningitis in childhood that was recently published (6), de Jonge et al. suggested that male gender is an important prognostic factor, a finding for which they do not have an explanation.

It is known that, even in animals (7), male gender predisposes to the development of shock in the form of, e.g., endotoxic shock in rats or in prepubertal acute respiratory distress syndrome (ARDS) patients with sepsis (1), a population in which an increased frequency (comparable to that of adults) of male patients is found. In contrast, the prognosis for females suffering from many inflammatory conditions (including those caused by infections but also those resulting from surgical procedures) has been shown to be better throughout life, whereas the prognosis for females is poorer when they suffer from chronic inflammatory diseases, such as cystic fibrosis (CF), severe asthma, or chronic pulmonary obstructive disease. In many infectious disease cases, C-reactive protein levels, erythrocyte sedimentation rate values, and neutrophil counts reached threshold levels above which values for girls were systematically higher than those observed with boys. With respect to the surgical stress of cardiac operations, females recover better than males (8), suggesting a more efficient inflammatory (and perhaps secondary anti-inflammatory) response in the face of similar levels of external insults that are limited in time and extent (e.g., those resulting from surgical trauma and extracorporeal circulation). In situations of greater complexity, such as those involving CF and autoimmunity, prognoses for females are poorer. We recently published three papers showing that the production of inflammatory markers (3) and the inflammatory process (4, 5) are clearly different for females and males. These observations could explain the male predominance in the results of the studies of Carr and de Jonge. In fact, inflammation is a double-edged sword. When patients are in good health, inflammation remains a very efficient process for avoiding important exogenous aggression of systemic life-threatening (as in the case of major thermal burns) or major local infections. In contrast, when inflammation persists, collateral deleterious effects of tissue destruction outweigh the initial advantage (as seen in cases of cystic fibrosis and lupus).

One possible explanation for these findings is that inflammatory reactions are driven by hormonal status. However, clinical data obtained before puberty imply the significance of potential differences in gene expression that depend on sexual chromosomes rather than on hormonal status, as members of prepubertal populations are largely immature and sexual hormones are far less abundant. Attention has recently been drawn to some rare genes on the X chromosome that are involved in the inflammatory cascade. As the silencing process for one of the X chromosomes is incomplete in females, some inflammation-related genes could therefore be overexpressed compared to the expression levels seen with males.

REFERENCES

1. **Bindl, L., et al.** 2003. Gender-based differences in children with sepsis and ARDS: The ESPNIC ARDS Database Group. Intensive Care Med. **29:**1770–1773.
2. **Carr, M. J., et al.** 2010. Molecular epidemiological evaluation of the recent resurgence in mumps virus infections in Ireland. J. Clin. Microbiol. **48:**3288–3294.
3. **Casimir, G. J., S. Mulier, L. Hanssens, K. Zylberberg, and J. Duchateau.** 2010. Gender differences in inflammatory markers in children. Shock **33:**258–262.
4. **Casimir, G. J., et al.** 2010. Chronic inflammatory diseases in children are more severe in girls. Shock **34:**23–26.
5. **Casimir, G. J., et al.** 2010. Gender differences and inflammation: an in vitro model of blood cells stimulation in prepubescent children. J. Inflamm. (London) **7:**28–34.
6. **de Jonge, R. C., A. M. van Furth, M. Wassenaar, R. J. Gemke, and C. B. Terwee.** 2010. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect. Dis. **10:**232.
7. **Losonczy, G., et al.** 2000. Male gender predisposes to development of endotoxic shock in the rat. Cardiovasc. Res. **47:**183–191.
8. **Seghaye, M. C., M. Qing, and G. von Bernuth.** 2001. Systemic inflammatory response to cardiac surgery: does female sex really protect? Crit. Care (London) **5:**280–282.

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Authors' Reply

We are very pleased to be given the opportunity to reply to the comments made by Casimir and Duchateau regarding our article "Molecular epidemiological evaluation of the recent resurgence in mumps virus infections in Ireland," published in the September 2010 issue of the *Journal of Clinical Microbiology* (2).

Potential factors contributing to the significant male bias for acute mumps virus infection reported in our recent paper are offered by Casimir and Duchateau in support of our findings. The main concepts discussed include response to vaccine, infection, inflammation, and autoimmunity, and the possible explanations indicated involve hormonal or genetic-chromosomal factors.

Two points are clear in the literature. First, males do not produce mumps antibody titers in response to two doses of measles, mumps, and rubella virus (MMR) vaccination that are as high as those seen with females, indicating gender-linked differences in humoral immune responses (5). It is now well recognized that immunity to mumps virus wanes, so it remains to be determined whether males show a sharper decline of mumps virus-specific antibodies than females. Our study showed a male bias for mumps virus infection in all age groups studied (data not shown), suggesting that hormonal status does not play a role. Second, several studies from Poland's group,

including studies involving twins, have shown an association of human leukocyte antigen (HLA) molecules with mumps vaccine-induced immune responses that may explain variations in mumps vaccine-induced responses (6).

Casimir and colleagues (3) have recently addressed gender influences on the production of cytokines involved in inflammation by studying healthy prepubescent males, females, and Turner's syndrome patients who have an XO genotype (X monosomy). Interestingly, although all Turner's syndrome patients are female, they showed the male pattern of reactivity, indicating a genetic-chromosomal influence.

Female predominance is a common characteristic in cases of autoimmune diseases postulated to be due to the combined effects of hormonal influences and genetic factors. The best evidence for hormonal effects on autoimmunity comes from pregnancy studies: when women are pregnant, disease activity subsides, but after delivery, disease exacerbation occurs. It is also well established that major histocompatibility complex (MHC) alleles are associated with disease susceptibility for most autoimmune diseases. More recently, several reports have found a role of X chromosome gene dosage in autoimmunity through inactivation and duplication (4). Furthermore, the role of genes located on the X chromosome in the immune system has been well documented in several primary immunodeficiency syndromes (1).

In conclusion, enhancing understanding of the genetic factors that influence immune responses to vaccine, infectious agents, or inflammatory insults would allow a better insight into mechanisms for the development of potential personalized vaccines (5) and therapeutic approaches.

REFERENCES

1. **Carneiro-Sampaio, M., and A. Coutinho.** 2007. Tolerance and autoimmunity: lessons at the bedside of primary immunodeficiencies. Adv. Immunol. **95:**51–82.
2. **Carr, M. J., et al.** 2010. Molecular epidemiological evaluation of the recent resurgence in mumps virus infections in Ireland. J. Clin. Microbiol. **48:**3288–3294.
3. **Casimir, G. J. A., et al.** 2010. Gender differences and inflammation: an in vitro model of blood cells stimulation in prepubescent children. J. Inflamm. **7:**28–34.
4. **Invernizzi, P., S. Pasini, C. Selmi, M. E. Gershwin, and M. Podda.** 2009. Female predominance and X chromosome defects in autoimmune diseases. J. AutoImmun. **33:**12–16.
5. **Ovsyannikova, I. G., et al.** 2008. Human leukocyte antigen and cytokine receptor gene polymorphisms associated with heterogeneous immune responses to mumps viral vaccine. Pediatrics **121:**1091–1099.
6. **Tan, P. L., R. M. Jacobson, G. A. Poland, S. J. Jacobsen, and V. S. Pankratz.** 2001. Twin studies of immunogenicity: determining the genetic contribution to vaccine failure. Vaccine **19:**2434–2439.

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