The Male:Female Ratio Does Not Explain a Higher Risk of Vertically Acquired Hepatitis C Virus Infection in Girls

To the Editor—Our work on risk factors for mother-to-child transmission of hepatitis C virus (HCV) was published in the December issue of the Journal of Infectious Diseases [1] with an accompanying editorial commentary by R. Palmer Beasley [2]. We showed that girls were twice as likely as boys to be HCV infected (adjusted odds ratio, 2.07 [95% confidence interval, 1.23–3.48]; P = .006) [1]. We would like to point out that the editorial contains a mistake: when discussing the possibility that this association could be due to excess male mortality in utero, Beasley erroneously calculates the male:female sex ratio from our data as 668:802, or 0.833. However, as shown in table 1 of our article, there were 802 boys and 668 girls, so the ratio would more likely be 802:668, or 1.20. This error explains why Beasley was unable to interpret our statement in the Discussion, “Because the male:female ratio in our study population was higher than that observed in the general population, this finding is unlikely to be due to excessive deaths of infected males in utero” (p. 1877).

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References


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References


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Reply to Seligman

To the Editor—We thank Seligman [1] for his discussion of the data we have presented [2]. We agree that the observed positive association between single nucleotide polymorphisms (SNPs) and susceptibility to West Nile virus disease comes with several caveats, and we took pains to explain these in our article. Given the similarity between the mean ages of the case patients and control subjects, it is not clear that a table stratifying age and allele frequency in these 2 groups would yield much useful information. Similarly, because the number of patients we studied was not large, we hesitated, as part of our analysis, to tabulate genotype and disease manifestations. Also, although a number of the novel SNPs appear to affect exon splice enhancers, they were observed at very low frequencies and lacked statistical significance. As a result, we did not draw any conclusions from these observations.

We agree that the door to a novel field has been opened, but we defer to the previously cited publications on flavivirus susceptibility in the mouse for its true origins [3, 4]. Additional work should target these variants in other diseases and conduct complete sequencing where possible, as a prelude to the protein and other functional studies that are recommended.

Potential conflicts of interest: none reported.
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impairment of the antipolysaccharide response in splenectomized patients is due to the lack of immunoglobulin m memory b cells

to the editor—in the abstract of their article entitled “administration of protein-conjugate pneumococcal vaccine to patients who have invasive disease after splenectomy despite their having received 23-valent pneumococcal polysaccharide vaccine” [1], musher et al. describe “2 patients who had recurring pneumococcal bacteremia after undergoing splenectomy despite having received numerous doses of ppv-23” (p. 1063). in the discussion, they say that “neither patient had ig to [polysaccharides], and each had at least 1 bout of overwhelming pneumococcal sepsis caused by a vaccine serotype” (p. 1066). interestingly, natural infection also failed to stimulate production of igg. heptavalent protein-conjugate pneumococcal vaccine (pcpv-7) was then administered, and it induced high levels of igg to all 7 polysaccharides. their finding raises interesting questions about the biological nature of the immune response to polysaccharide antigen.

recently, we studied the biological mechanisms responsible for the increased susceptibility to encapsulated bacterial infections in several clinical conditions. although our understanding of human b cell development and b cell subsets is still limited, some relevant pieces of the puzzle are already in our hands. here, we summarize our findings on human b cell defense against pneumococcal infection.

we first demonstrated in the mouse that b-1a b cells, derived from fetal liver precursors, require the spleen for their survival; they produce natural and antipolysaccharide antibodies ensuring the first line of protection against streptococcus pneumoniae infection [2]. our strategy to identify the human counterpart of murine b-1a b cells was based on the assumption that the increased susceptibility to s. pneumoniae infections and the poor response to polysaccharide antigens may be associated with the lack of a defined b cell population in individuals at a high risk of developing pneumococcal diseases, such as splenectomized and asplenic patients, children <2 years of age, and patients with primary humoral immunodeficiencies. the common denominator in all these groups is the lack of igm memory b cells [3], a population identified by the expression of cd27, igm, and igd that accounts for one-third of peripheral b cells. the expression of the memory marker cd27 and the presence of somatic mutations led to their classification as memory cells [4]. memory b cells are the most sophisticated actor in the adaptive immune response: in the germinal centers, after immunization or infection, b cells proliferate and accumulate somatic mutations, changing their affinity to the stimulating antigen. the final products of the germinal center reaction are high-affinity memory b cells. several lines of evidence indicate, however, that a subset of b cells, the so-called igm memory b cells, can be generated in the absence of germinal centers [5]. moreover, their frequency in the blood correlates with the concentration of igm to pneumococcal polysaccharides [3].

human igm memory b cells cannot be detected in splenectomized and asplenic individuals, and their absence is associated with an increased frequency of pneumococcal infections and impaired response to polysaccharide vaccines. we concluded that the spleen is indispensable for the generation or survival of igm memory b cells and for protection against encapsulated bacteria.

it is not known whether the spleen is the unique site where igm memory b cells are generated or represents the environment where igm memory b cells survive and produce antibodies. igm memory b cells produce natural antibodies and are necessary for the t-independent response against polysaccharides of encapsulated bacteria [3]. the absence of igm memory b cells correlates with an impaired immune response to encapsulated bacteria not only in splenectomized patients but also in individuals with an intact spleen. we showed that the physiological and transient predisposition to pneumococcal infections of young children (0–2 years of age) is associated with a lack of circulating igm memory b cells and of serum antipolysaccharide igm [3]. the polysaccharide vaccine against s. pneumoniae contains a mixture of capsular polysaccharides from the 23 most frequent bacterial serotypes and induces antibody production only if administered before splenectomy, but it is ineffective if the spleen has been already removed [6]. it is not protective in children younger than 2 years of age. to circumvent the physiological and transient lack of response to polysaccharides, polysaccharide–protein conjugate vaccines have been developed. in young children, pcpv-7 reduces the risk of systemic pneumococcal infection by >90% [7]. by eliciting a classic t-dependent immune response, they bypass the immunological impairment caused by the lack of igm memory b cells. similarly, the administration of conjugate vaccines may reduce the risk of systemic infections, including overwhelming pneumococcal sepsis, after splenectomy, musher et al. propose in their article [1]. our data provide

references
