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COMMENTARY

A plausible explanation for male dominance in typhoid ileal perforation

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Abstract: The phenomenon of consistent male dominance in typhoid ileal perforation (TIP) is not well understood. It cannot be explained on the basis of microbial virulence, Peyer's patch anatomy, ileal wall thickness, gastric acidity, host genetic factors, or sex-linked bias in hospital attendance. The cytokine response to an intestinal infection in males is predominantly proinflammatory as compared with that in females, presumably due to differences in the sex hormonal milieu. Sex hormone receptors have been detected on lymphocytes and macrophages, including on Peyer's patches, inflammation of which (probably similar to the Shwartzman reaction/Koch phenomenon) is the forerunner of TIP, and is not excluded from the regulatory effects of sex hormones. Hormonal control of host-pathogen interaction may override genetic control. Environmental exposure to *Salmonella typhi* may be more frequent in males, presumably due to sex-linked differences in hygiene practices and dining-out behavior. A plausible explanation of male dominance in TIP could include sex-linked differences in the degree of natural exposure of Peyer's patches to *S. typhi.* An alternative explanation may include sexual dimorphism in host inflammatory response patterns in Peyer's patches that have been induced by *S. typhi*. Both hypotheses are testable.

Keywords: explanation, dominance, male, perforation, ileum, typhoid

Introduction

Typhoid fever caused by *Salmonella typhi* is a systemic illness in which the portal of entry is the gastrointestinal tract. Ileal perforation, which occurs in 1%–17% of cases of typhoid fever, is a serious complication.[1] Male dominance in patients with typhoid ileal perforation (TIP) is well recognized.[2,3] A recent study has confirmed earlier observations that males with typhoid fever are at increased risk of developing TIP.[4–6] The phenomenon of male dominance in TIP is not well explained.

Pathogenesis of TIP

Tissue reactions to *S. typhi* leading to TIP are probably similar to the Shwartzman reaction/Koch phenomenon.[7] Central to the Shwartzman reaction/Koch phenomenon are exaggerated inflammatory reactions upon re-exposure to a particular antigen (eg, lipopolysaccharides of *S. typhi*), leading to cell necrosis at a tissue site already primed by prior exposure to the same antigen. In typhoid fever, exposure and re-exposure of Peyer's patches to *S. typhi* occurs, respectively, when the ingested *S. typhi* breaches the intestinal barrier via M cells overlying the Peyer's patches and bacteria multiplied in the liver enter into the intestinal lumen via biliary passage.[7] Cytokines, eg, tumor necrosis factor alpha, produced by induced macrophages and mononuclear

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cells in Peyer's patches, mediate ulceration and cell necrosis, leading to TIP.[7,8]

Current views on male dominance in TIP

Typhoid fever is more frequent in males, and this is a notion based on observations made in patients hospitalized with typhoid fever. There is also the notion of sex bias in the utilization of health services in the direction of males. However, each notion has pitfalls. Male dominance in hospitalized patients with typhoid fever is not consistent.[9] While an infection (eg, *Yersinia enterocolitica* diarrhea) may be more common in males, a particular pattern of host response to it (eg, erythema nodosum) may show a predilection for females.[10,11] In many developing countries, the perceived severity of illness is one of the most important factors for attending hospital.[12] The majority of patients with TIP are brought to hospital with fulminating generalized peritonitis after several days of attempted self-medication at home. It is difficult to imagine how a woman with TIP would be left alone by her family members to die, given that, from child rearing to cooking and assisting on farms, women are important and productive members of the household in many communities in which typhoid fever is endemic.[13]

Plausibility of sexual dimorphism in host response to *S. typhi* infection

Natural priming of Peyer's patches occurs due to repeated contact with subinfecting doses of *S. typhi*.[14] Whether inside or outside the home environment, males seem to be at greater risk of exposure to *S. typhi* than females, presumably due to less adherence by males to hygiene measures, including hand washing before handling food and eating, hygienic defrosting practices, and the greater propensity of men to eat raw or undercooked foods and at roadside locations.[9,15–22] This raises the possibility that levels of natural exposure to *S. typhi* in typhoid-endemic areas may be different between males and females.[7] Pathologically, this would mean that in the event of re-exposure to *S. typhi*, the inflammatory reaction at Peyer's patches, which is the forerunner to TIP, may be stronger in men than in women.

Studies in humans as well as in animals have shown that during the course of an intestinal infection, males show a predominantly proinflammatory cytokine response (eg, interleukin-6, tumor necrosis factor alpha, and macrophage inflammatory protein-2). In contrast, females show a predominantly anti-inflammatory cytokine response (eg, interleukin-10).[23] This may mean that the female intestine is more resistant than the male intestine to damage in response to an inflammatory process induced by a microbial challenge. The biological basis of sexual dimorphism, as suggested above, in the host cytokine response to an infection can be explained on the basis of the dominance of estrogens over androgens in females and androgens over estrogens in males. Of note, sex hormone receptors have been detected on lymphocytes and macrophages, and Peyer's patches cannot be excluded from the regulatory effects that sex hormones exert on immunity.[24,25]

Epidemiological studies have demonstrated that, in general, for a given infection, boys have a significantly higher incidence of severe infection than girls.[26] In typhoid fever, the development of bowel perforation does indicate severe disease.[27] As in adults, the sex hormonal milieu is different in boys and girls, as evidenced by higher levels of estrogens in girls before puberty.[28,29]

Anatomical and physiological considerations

A carefully executed morphometric study did not find any sex-linked difference in the anatomy of human Peyer's patches.[30] Distension of the intestine is common in typhoid fever. The degree of stress it produces on the bowel wall, already weakened by ulceration, is directly related to the luminal diameter (according to LaPlace's law). However, in adults as well as in children, there is no difference between males and females in terms of luminal diameter and thickness of the bowel wall.[31,32] There is also no sex-linked difference in gastric acidity in adults or in children.[33,34] Of note, gastric acidity provides the first-line bactericidal barrier to *S. typhi* within the gastrointestinal tract. This means that for a given number of *S. typhi* ingested, the number of bacteria entering the duodenum might not be different between males and females. This is important, because the dose of *S. typhi* ingested is directly related to the severity of typhoid fever.[35]

Microbial factors

Strain variations in *S. typhi* may explain variations in the severity of typhoid fever. Although lacking in consensus, such variations have been advanced to explain geographic variations in the severity of typhoid fever.[35,36] However, in the absence of preferential exposure of a particular gender group to a newly emergent or imported strain of *S. typhi*, it is inconceivable how such variations would explain sex-linked bias in the incidence of TIP in patients with typhoid fever who are living in the same endemic area. *S. typhi*-infected

macrophages do show features of apoptotic cell death.[7] However, this alone would not explain the development of extensive ileal ulceration of varying severity, which is almost the rule in the natural history of typhoid fever.[37,38] This is because only 0.1% or less of cells in Peyer's patches are macrophages.[14] It is questionable if *S. typhi* is directly necrotic to human enterocytes, ie, the cells lining the intestine, because *S. typhi* is too sophisticated and well adapted to its only natural host (ie, humans) to preside over its own extinction.[39] As an additional survival strategy, *S. typhi* has evolved mechanisms to downregulate the inflammatory response it may induce in its host.[40] There is nothing intrinsically poisonous about this endotoxin; what is important is the host response to it.[41,42]

Genetic host factors

Deletions, mutations, or absence of genes encoding major proteins in the type 1 cytokine (eg, interferon gamma) have been linked to host susceptibility and patterns of response to intracellular bacteria such as *Mycobacterium tuberculosis* and nontyphoidal *Salmonella*.[43] Such variations are inconsistent and restricted to certain groups of individuals and certain geographic areas, eg, interleukin-12p40-deficient individuals in Saudi Arabia. They are neither present at the population level nor predominant in a particular gender group, even in a single well defined geographic area. Male dominance in TIP is consistent and observed in all typhoid endemic areas. Of fundamental importance is the possibility that hormonal control of immunity to infection may override genetic control.[44,45]

Plausible explanation for male dominance in TIP

A plausible explanation for male dominance in TIP may include differences in levels of background exposure of males and females to *S. typhi*. Alternatively, possible sexual dichotomy, as above, in the host cytokine response at the site of localization of *S. typhi* in Peyer's patches may explain the male dominance of TIP. This could be tested experimentally.

The first part of the protocol (Figure 1) will address whether there is any sex-linked difference in the levels of natural exposure to *S. typhi*. Prima facie evidence can be obtained by serosurveys, measuring the prevalence of antibodies to *S. typhi* Vi and H antigens in otherwise healthy males and females of different age groups with no history of having received antibiotics 8 weeks before enrolment in the study or typhoid vaccination.[46–48] Multiple stool and duodenal aspirate samples can be obtained in subjects who react positively to one of the abovementioned serological tests. These samples can then be tested as outlined in Figure 1. For more convincing evidence, tissue samples can be obtained at autopsy from the mesenteric lymph nodes in otherwise

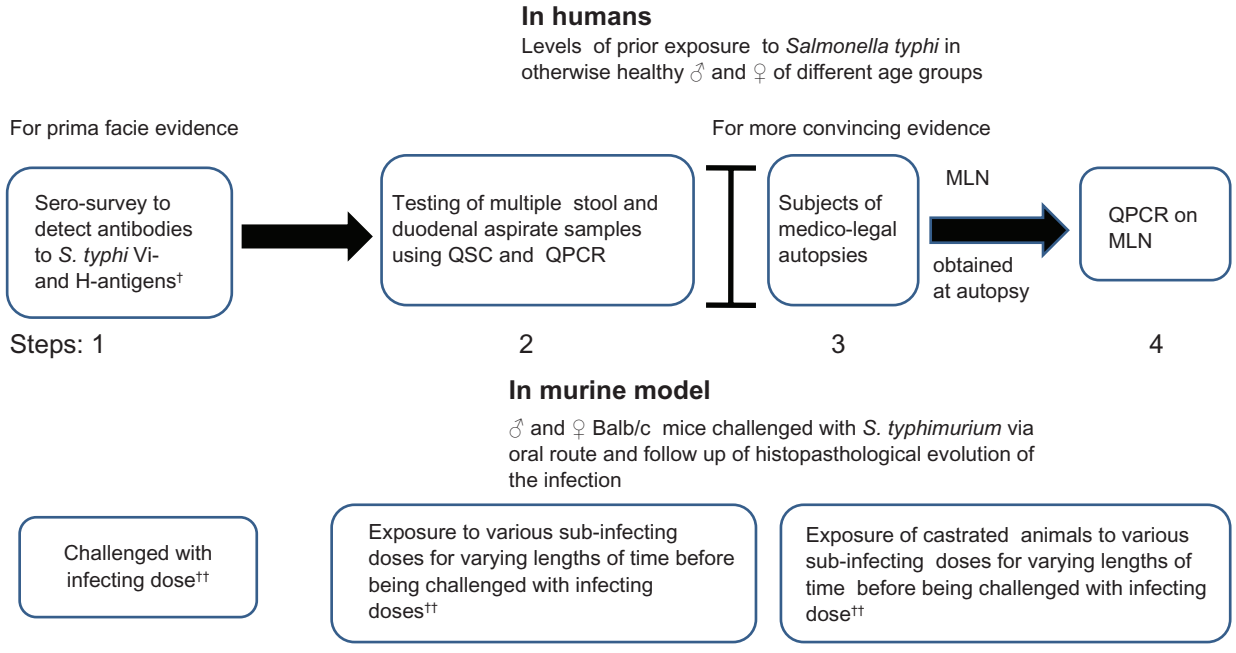

Figure 1 A schemata for testing that male dominance in typhoid ileal perforation may be due to: (a) differences in the levels of environmental exposure (via oral route) of male and female to *Salmonella typhi* or (b) sexual dichotomy in host's tissue reactions at the site of localization *S. typhi* in the Peyer's patches.
Notes: †See the text for exclusion criteria; ††same infecting dose for all animals.
Abbreviations: QSC, quantitative stool culture; QPCR, quantitative polymerase chain; MLN, mesenteric lymph nodes.

healthy males and females of different age groups who are cases of accidental death or subject to medicolegal autopsy. In *S. typhi* infection, the mesenteric lymph nodes are invariably involved once the organism breaches the intestinal epithelial barrier.[49] Infection can persist at these tissue sites for months without producing any clinical signs and symptoms. The number of bacilli in a single mesenteric lymph node may be as few as ten.[49] Quantitative polymerase chain reaction can be used for quantitative analysis of the presence of the organism in the mesenteric lymph nodes. There is the possibility that the vaccine strain of *S. typhi* used in the oral typhoid vaccine formulation might breach the intestinal mucosal barrier.[50] This potential source of differential contamination should be excluded when interpreting the results of the quantitative polymerase chain reaction.

An animal model would be necessary to examine the host cytokine response and degrees of histopathological changes at Peyer's patches that have been primed by repeated prior exposures to subinfecting doses of *S. typhi* before being exposed to an infecting dose of *S. typhi*.

S. typhi is a human host-specific parasite, and there is no ideal animal model for typhoid fever.[51] The best characterized animal model of typhoid fever is the murine one, although this model relies on a surrogate pathogen (ie, *Salmonella typhimurium*) and a surrogate host (ie, Balb/c inbred mice).[7] In the murine model, the disease can be induced via the oral route with clinical and laboratory signs, including ulceration of Peyer's patches resembling that associated with typhoid fever in humans.[52] Once in the mesenteric lymph nodes, *S. typhimurium* can persist at this site for months without producing any signs or symptoms of disease.[53]

In one arm of the experiment, aged-matched male and female mice of different age groups would be challenged with *S. typhimurium* to produce clinical disease. In another arm of the experiment, male and female animals would be exposed to subinfecting doses of *S. typhimurium* over a varying period of time before being challenged with an infecting dose of *S. typhimurium*.

In summary, a plausible explanation for male dominance in TIP may include differences in the levels of natural exposure of males and females to *S. typhi*. An alternative explanation may include sex-linked differences in the host inflammatory response induced by *S. typhi* at Peyer's patches. Both hypotheses are testable.

Disclosure

The author reports no conflicts of interest in this work.

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