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**BAGER P, Vinkel Hansen A, Wohlfahrt J, Melbye M, et al.
Helminth infection does not reduce risk for chronic inflammatory
disease in a population-based cohort study. *Gastroenterology*.
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Joel V. Weinstock, MD

Chief of the Division of Gastroenterology/Hepatology, Tufts Medical Center, and Professor at
Tufts University

Summary

Childhood infections with some helminths have been reported to reduce the risk of acquiring some immune-mediated diseases like sensitization to allergens, asthma and inflammatory bowel disease. Denmark keeps a medical registry that collects data on disease prevalence and medication use throughout the country. Mebendazole frequently is used to treat pinworm (*Enterobius vermicularis*) infection. In this population-based analysis of a cohort of 924,749 children, prescriptions for Mebendazole were used as a surrogate marker for pinworm infection. Children who received this medication were compared to children who did not, for the frequency of asthma, type I diabetes, juvenile arthritis, ulcerative colitis and Crohn's disease. It was found that Mebendazole use, and by inference pinworm infection, did not appear to reduce the risk for acquiring any of these immune-mediated diseases.

Comment

Once considered rare, IBD is common in people living in developed countries, and it is spreading into underdeveloped countries experiencing rapid improvements in life-style. The “*IBD hygiene hypothesis*” was proposed to explain these rapid changes in IBD prevalence. (1) It stated that modern day living changed intestinal flora and fauna and that this change impaired the development of the immune regulatory circuits that previously protected us from IBD and other such immune-mediated diseases. It also was proposed that loss of helminthic infections was particular important because of their strong stimulatory influence on host immune regulatory circuits.

The article (2) addresses the issue of whether pinworm exposure is associated with a lower frequency of IBD or several other immune related disease in young people. Although the data provided are interesting, they are of limited value and are inadequate to support the broad conclusion that helminthic colonization does not reduce the risk for various immune-mediated diseases.

The uncertainty of the diagnosis seriously compromised this investigation. It was not possible to know if patients treated with Mebendazole were actually infected with pinworm. Testing methods for pinworm infection are limited. Pinworm cannot be diagnosed using serological techniques or by examining the stool for ova or adult worms. Physicians

frequently make the diagnosis based on patient symptoms rather than using the cumbersome “cellophane tape” test. Diagnosis based on symptoms is not dependable, which almost certainly was the approach used for diagnosis in Denmark. A recent study from Nigeria highlights the difficulty in diagnosis and the unreliability of the diagnostic tests. (3) Patients with pinworm usually have little or no symptoms. While pruritis ani is the most common symptom, the vast majority of patients with pruritis ani do not have pinworm infection. It is common practice to treat family members of patients with presumed pinworm infection on the unproven assumption that they too have the infection. Moreover, since there was no definitive diagnosis, it is possible that some symptomatic patients actually had conditions like early inflammatory bowel disease.

The duration of helminthic exposure may be a critical variable in the prevention of immune-mediated disease. If the infection is asymptomatic, which is usually the case, the diagnosis will not be made, and the infection will remain untreated perhaps for many years. Symptomatic individuals would receive immediate medical attention and would perhaps have had very limited duration of exposure. It was not possible to control for this potentially critical variable in this study.

The title of the paper extends beyond the experimental results. The study focused on the possible protective role of pinworm infection with regard to immune related diseases, but did not address the potential importance of other helminths in the protective process as inferred by the title. It cannot be assumed that all helminthic species induce similar immunological responses. For instance, a recent human case control study from India supports a role of helminths in the hygiene hypothesis in Crohn’s disease.(4) It demonstrated that a lower frequency of exposure to hookworm, as determined by a serological marker of infection, was associated with a higher frequency of Crohn’s disease. Pinworm, hookworm, whipworm, and schistosomes, for instance, are distinct species.

In conclusion, the study addressed an important issue, but its execution displays several important weaknesses:

- The failure to definitively diagnose pinworm infection may have led to wrong conclusions.
- The duration of pinworm infection may be an important variable in inducing immune modulation and could not be controlled in this study. Also, subjects with “silent” infection were in the control group.
- Pinworms may be inferior to other helminths in inducing effective immune modulatory effects. Thus, the title of the paper and some of the general conclusions outpace the actual data presented.

The paper also illustrates the difficulty in studying the epidemiology of helminthic infections. The tools required to perform such studies are limited, and helminths are stealthy creatures that often leave few footprints after the infection clears.

There is a growing body of evidence that helminths suppress aberrant inflammation. Animal models of disease also strongly support an important protective role of helminths through

induction of regulatory immune circuits. (5,6) Many epidemiological studies demonstrate the relevance of this hypothesis in several disease states. (7) The data presented in the Bager paper are quite limited and not conclusive. However, there is a study reporting that “hygiene” in children may not protect children from IBD.(8)

Translation of helminthic infections into therapeutic vaccines is the logical consequence of clinical and experimental observations supporting this hypothesis. Several published clinical trials support their efficacy in IBD. (9,10,11,12,13)

Currently, there are United States (NCT01576471) and European (NCT01279577) multicenter double-blinded placebo-controlled trials testing the efficacy and safety of *T. suis* for induction of remission in Crohn’s disease. The European study passed interim analysis and is projected to conclude sometime in 2013. There also is approval for an investigator initiated study using *T. suis* ova for induction of remission in ulcerative colitis (NCT01433471). Other diseases are under study as well.

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