Inflammatory Intestinal Diseases

Inflamm Intest Dis 2016;1:147–149
DOI: 10.1159/000455177

Published online: February 1, 2017

Autoimmune Hepatitis in the East and the West

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Autoimmune hepatitis (AIH) is a chronic progressive liver disease characterized by unresolving inflammation of the liver, hypergammaglobulinemia, production of autoantibodies, characteristic histological features of lymphoplasmacytic interface hepatitis, and responsiveness to immunosuppression [1, 2]. It is a serious condition that is associated with at least a 2-fold higher mortality than that of the general population [3, 4]. Although it is understood that there is an autoimmune basis to the pathogenesis of AIH, its precise etiology remains unknown. Epidemiology is an important part of etiologic research, as information gained from epidemiological studies can be a powerful tool by which to gain important insights into the disease. The current working model postulates that environmental triggers, a failure of immune tolerance mechanisms, and a genetic predisposition collaborate to induce an uninhibited T cell-mediated immune attack upon hepatocytes [5]. In this issue, Enomoto et al. [6] have provided an excellent summary of the similarities and differences in the epidemiology of AIH between the East and the West.

The establishment of the standardized AIH diagnostic criteria by the International AIH Group has ensured consistent case definitions in AIH research, providing a meaningful comparison of AIH studies conducted in different parts of the world [7, 8]. It is interesting to note that the incidence and prevalence of AIH are consistently reported as lower in the East than in the West as summarized by Enomoto et al. [6]. In the West, the prevalence of AIH was reported as 15–25 cases per 100,000 inhabitants, whereas much lower rates of 4–5 cases per 100,000 inhabitants were reported in the East [9]. Comparing the prevalence and incidence from different regions is not always easy, as the methodology and quality of the studies may have a profound effect on the results. For example, an ineffective case identification methodology would inevitably lead to an underestimation of prevalence and incidence rates. Therefore, one could question whether the lower AIH prevalence in the East could solely be explained by the paucity of high-quality population-based AIH studies. Interestingly, a population-based study performed in New Zealand has convincingly shown that the AIH prevalence is indeed different between various ethnic groups that reside in Canterbury [10]. This study shows that Caucasians have a significantly higher AIH prevalence (28 per 100,000) than Asians or Maoris (5–7 per 100,000) in Canterbury despite being exposed to similar environmental factors. This result suggests that the

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observed difference in prevalence rates between the East and the West is likely real and that genetic predisposition is a factor in the pathogenesis of AIH.

A genome-wide association study performed in the Netherlands has identified *HLA-DRB1*0301* as a primary susceptibility genotype and *HLA-DRB1*0401* as a secondary susceptibility genotype; about 70% of the AIH patients included had either [11]. This finding is in agreement with several earlier studies from the West. In addition, *HLA-DRB1*0301* is also found to be the strongest genetic modifier of disease severity in type 1 AIH, as *HLA-DRB1*0301*-positive AIH patients tend to exhibit a more severe disease phenotype [12]. However, both of these genotypes are rarely found in AIH patients from the East. It is also interesting to note that the frequency of *HLADRB1*0301* is found to be much higher in European ancestry populations than in Asians [13]. It is likely that a low frequency of a disease susceptibility genotype, such as *HLA-DRB1*0301*, in Asians, among other factors, may have contributed to a lower AIH prevalence in the East.

While it is undeniable that genes play a role in the pathogenesis of AIH and are responsible for some differences observed between AIH patients in the East and the West, they are certainly not the only factor, and likely not the most important one either. This is demonstrated by the very low prevalence of AIH of only 0.2% in first-degree relatives of AIH patients [14]. Indeed, the vast majority of AIH patients do not have a family history of the disease. In addition, a study from Denmark has nicely demonstrated that the incidence of AIH is increasing steadily [15]. These findings suggest that environmental factors may have an important influence on the pathogenesis of AIH. The use of certain medications, such as nitrofurantoin and minocycline, is well known to induce AIH. In the East, herbal medicines have also been reported to cause AIH. Unfortunately, studies that systematically examine the association between AIH and other important environmental factors, such as diet and lifestyle, remain sparse. Comparative studies between the East and the West that address these important issues should be conducted, as they could help to identify modifiable lifestyle risk or protective factors and to provide important insights into the etiology of AIH.

There are case series which suggest that Asian-American and African-American AIH patients present with more aggressive disease and have poorer survival than Caucasians [16, 17]. However, a more recent comparative study shows that responses to treatment and survival in Asian and Caucasian AIH patients are similar [18]. This study also found that Asians tend to present at an older age with jaundice and have a low positivity of smooth muscle antibodies. These results suggest that ethnicity likely has an impact on the natural history of AIH, but they also highlight the need for high-quality comparative studies between different regions.

Enomoto et al. [6] have shown that, while there are many similarities between AIH in the East and the West, differences exist. The prevalence is lower in the East than in the West, and genetic differences may have contributed to some of the observed differences. Environmental factors, such as diet and lifestyle, are likely to have an important influence on the pathogenesis of the disease, yet information on these issues is sparse. New high-quality comparative studies between the East and the West are desperately needed.

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