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Review Article

Geographical Disparity in Primary Biliary Cholangitis Prevalence: A Mini-review

I Dewa Nyoman Wibawa[1*] and Christina Permata Shalim[2]

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, Indonesia;* [2]*Siloam Hospitals Kebon Jeruk, Jakarta, Indonesia*

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Abstract

Primary biliary cholangitis (PBC) has been shown to occur more often in the West than in the East. The reason for this geographical disparity remains to be determined. Some researchers have considered that this was merely due to the lack of awareness on PBC in the East. Thus, the reported case and epidemiological studies on this disease remain scarce in the East. Other studies have suggested genetic predisposition and environmental factors proven to play important roles in the disease pathogenesis. In addition, these might also cause the disease to be more susceptible in some populations. The findings reported by multiple genome-wide association studies (GWAS) in recent years have not yet identified the specific genes responsible for the development of PBC, with different susceptible genes identified on each study in different regions. The present review describes some factors that might be associated with this geographical disparity.

Introduction

Primary biliary cholangitis (PBC), which is formerly known as primary biliary cirrhosis, is a chronic autoimmune cholestatic liver disease that can lead to cirrhosis and liver failure.[1] The diagnostic criteria for PBC requires at least two of these three criteria: the presence of elevated cholestatic liver enzymes, the presence of serum antimitochondrial antibodies (AMA), and lymphocytic infiltration/granulomatous destruction of the interlobular bile ducts on liver biopsy.[2] This disease is female predominant, with a 9:1 female-to-male ratio, and frequently develops at approximately 40–60 years old.[3]

Based on available epidemiological studies, PBC was identified to be more common in Western populations, when compared to the Eastern population. The reason for this geographical disparity remains to be determined. The present review describes some of the possible explanations for this geographical disparity, providing inputs for future researches in determining the factors that influence this phenomenon.

Keywords: Primary biliary cholangitis; Prevalence; Risk factor; Geographical.

Abbreviations: AMA, antimitochondrial antibodies; MHC, major histocompatibility complex; GWAS, genome-wide association studies; PBC, primary biliary cholangitis; PDC-E2, pyruvate dehydrogenase complex E2 subunit.

[*]**Correspondence to:** I Dewa Nyoman Wibawa, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, Indonesia. ORCID: https://orcid.org/0000-0001-5190-3072. Tel: +62 361466427, Fax: +62 361235987 , E-mail: agusbobwibawa@yahoo.com

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Epidemiology

The global prevalence and incidence of PBC varies widely by geographic area.[4,5] Most epidemiological data on PBC were obtained from studies conducted in Europe. Based on the data available from published studies, the identified regions with the highest prevalence of PBC are Northern Europe and North America, with a prevalence of approximately 28.3–46.5 per 100,000 population. However, few epidemiological studies on PBC have been conducted in Asia. That is, these are only available in some countries, including Japan, Hong Kong, and South Korea. Overall, its prevalence was much lower than that observed in European countries, with an estimated prevalence of 11.87 per 100,000 population in the Asia-Pacific region. PBC is presently considered as a rare disease in the East (Fig. 1).[6] However, some reports have revealed an exception. A study conducted in Japan revealed that the prevalence of PBC in 2016 was 33.8, which was comparable to that in the West. However, the prevalence of PBC in Japan in 2004 was 11.6, showing that the prevalence almost tripled.[7] It is possible that this increasing trend of PBC also occurred in other countries in Asia.

Etiology

The etiology of PBC remains unknown. However, it is presently considered that this has an autoimmune process, with the presence of serum AMAs and autoreactive T cells in the majority of cases.[8]

AMA targets the members of the 2-oxo-acid dehydrogenase complexes, including pyruvate dehydrogenase complex E2 subunit (PDC-E2), branched-chain 2-oxoacid dehydrogenase complexes, and 2-oxoglutarate dehydrogenase complexes. These enzymes

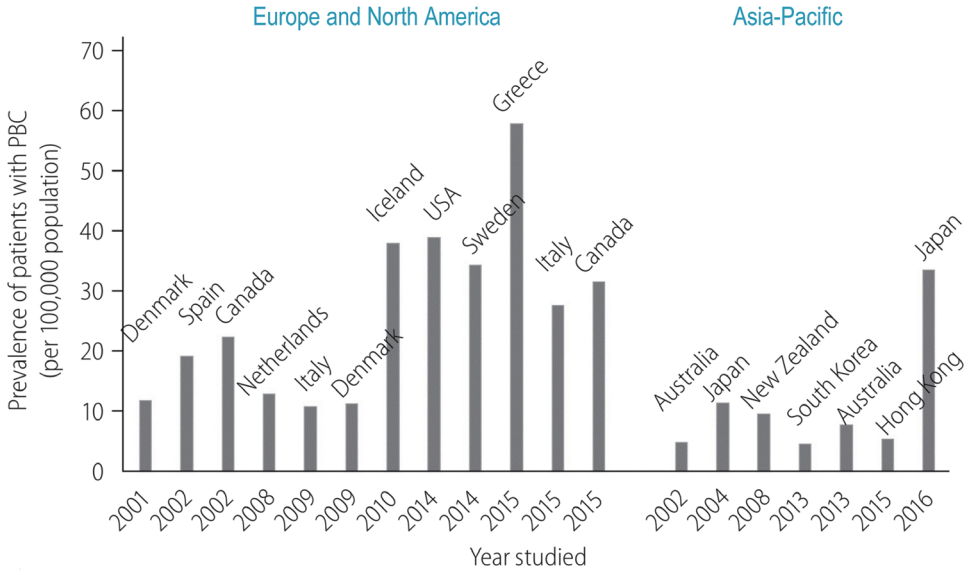

Fig. 1. Prevalence of PBC over time, and in different geographical regions (per 100,000 population).[6] PBC, primary biliary cholangitis.

are located in the inner mitochondrial membrane, and catalyze the oxidative decarboxylation of ketoacid substrates.[9]

Some studies have attempted to determine the factors that contribute to the development of PBC. Genetic predisposition and environmental factors were presumed to be important in the disease development.

Several genome-wide association studies (GWAS) have been conducted in recent years to identify the specific susceptible genes responsible for the development of PBC. However, these studies did not provide satisfying results. That is, for the risk genes identified to contribute to the susceptibility of PBC, it appears that these merely contributed to approximately 15% of the heritability of PBC.[10] Thus, hypothetically, other factors, in addition to genetic factors, play a major role in the pathogenesis of PBC.

Epigenetics, which comprises modifications of the gene expression that do not involve the DNA sequence, and creates phenotypic changes that are stable and can be inherited, might explain the lack of heritability of PBC, based on genes alone.[3]

Genetic factors

The relative risk for siblings of PBC patients was 10, and the risk rose to 35 for the daughters of patients with PBC, thereby presenting the immune abnormalities that were inherited.[1]

The associations of autoimmune diseases with specific major histocompatibility complex (MHC) alleles have also been reported. It was proposed that the polymorphic variant of the MHC might enhance the recognition of a self-peptide. When the self-peptide-MHC complex interacts with the host T cell, this would influence the immunogenicity. For PBC, numerous studies have reported the specific associations of class I, II and III MHC alleles in PBC patients, even though this association was considered as weak.[11]

Environmental factors

Several studies have revealed that some environmental factors might be associated with the development of PBC. Large-scale case-control studies have revealed that urinary tract infection and cigarette smoking are the most influential in developing PBC.[12]

Escherichia coli (*E. coli*), which is a major pathogen in women with urinary tract infection, has been shown to be a strong inducer of PDC-E2-specific AMA and liver pathology, consistent with the PBC in the mouse model. This finding suggests that in genetically susceptible hosts, *E. Coli* infection may indeed trigger PBC. *E. coli* most likely leads to the development of PBC through molecular mimicry. Human PDC-E2 shares a significant homology with *E. coli* PDC-E2, particularly in regions of the immunodominant epitopes of AMA. The similarity between human PDC-E2 and *E. coli* PDC-E2 might explain the disruption of tolerance to mitochondrial autoantigens, and the development of AMA.[13]

The immunomodulatory effects of cigarette smoking are diverse, including the increase in proinflammatory cytokines IL1, IL6, IL8 and TNFα. The chronic inflammation and widespread cellular damage induced by cigarette smoking can trigger pathogenic adaptive Th1 immune responses against various cellular antigens, and disturb the regulation of T cell homeostasis. This is consistent with PBC, in which Th1 cells are the predominant infiltrating lymphocytes, and the T cell compartment function is underregulated.[14]

Other chemicals that can be found in daily life, such as lipsticks, hair dyes and nail polish, have also been considered to have a role in producing immunogenic neoantigens, triggering PBC.[12,15]

Epigenetic modifications

There are three known mechanisms for epigenetic modifications: DNA methylation, histone modification, and modification via non-coding RNAs. Most available studies on the epigenetic modifications of PBC have focused on the methylation of the X chromosome in PBC, and on small and noncoding RNAs (ncRNAs), particularly microRNAs (miRNAs).[16]

Even though the reason for the female predominance in PBC remains unclear, studies have revealed that alteration in the structure of the X chromosome might play a major role. The results for the genome-wide analysis conducted by Selmi *et al.* on the female monozygotic twins discordant for PBC revealed that 60 differentially methylated regions were affected, when compared to the unaffected twin, with 51 genes on the X chromosome. This finding is consistent with the female predominance of PBC.[17]

NcRNAs are functional RNA molecules that are not translated into protein. MiRNAs, included in ncRNAs, regulate major cellular processes, such as apoptosis, differentiation, cell cycle, and immune functions. Based on several studies, various miRNAs are dysregulated in PBC, and this dysregulation leads to the development and progression of PBC.[18,19]

Geographical disparity in PBC prevalence

It remains debatable why the prevalence of PBC in the East is much lower than that in the West. Some researchers have considered that this was due to the lack of awareness of PBC in some Asian countries, who were getting better in recent years, thereby making the reported cases higher.

Most studies that reported the epidemiology of PBC are retrospective studies. The frequently identified problem is the different approaches in identifying cases obtained from medical records. A number of studies use the presence of AMA as the key diagnostic feature. However, in reality, approximately 5–10% of PBC patients are AMA negative, thereby resulting in misdiagnosis and underreported cases.[20]

The factors mentioned above, which influence the development of PBC, such as genetic predisposition and environmental factors, might also play a crucial role on the different prevalence of PBC in the East and West. Some HLA class 2 alleles were identified to be associated with PBC in limited geographical areas. A study conducted in Newcastle, United Kingdom revealed that the linkage of DQA1*0401 and DR8-DQB1*0402 is associated with PBC progression, but not susceptibility.[21] However, the results obtained from several other studies conducted for different non-British European populations did not confirm this association. A study conducted in Japan revealed the significant associations between DRB1*08:03-DQB1*06:01 and DRB1*04:05-DQB1*04:01 haplotypes with PBC susceptibility.[22]

Multiple GWAS on PBC conducted for Japanese, European, and Han Chinese populations revealed that some of the susceptible genes overlap in these three populations (CD80, STAT4, NF-êB1 and 17q12–21), even though there were also differences, in terms of which genes have the strongest association with PBC.[23]

Some environmental factors that trigger the development of PBC, such as cigarette smoking and toxin exposure, were more common in the West. However, in recent years, these have been more equally shared by the East and West, and this might also explain the lower prevalence of PBC in the East, especially in the past, and the recent increase in prevalence of PBC in the East.[15]

The epigenetic studies mentioned above might also explain the geographical disparity. It is possible that populations with a high prevalence of PBC not only have more susceptible genes, but also are more prone to the epigenetic process of developing PBC, in which environmental triggers surround these. However, no specific study regarding this topic has been found, to date. Studies on the epigenetic process of PBC have mostly focused on its effect on female predominance, and no study has investigated its effect on the differences in prevalence in different regions, especially between the East and West.

Conclusions

The definite explanation on why a disparity in PBC prevalence exists among the East and West regions remains debatable. Based on previous researches, there are a few possible explanations. First, there was a lack of awareness and studies on PBC in some Asian countries, who were just getting better in recent years, thereby leading to underreported cases. Second, there was a small percentage of patients with AMA negative. Hence, this has not been well-studied. Third, it was considered that the unique and complex genetic and environmental interplay can influence and trigger the development of PBC. These genetic and environmental factors (mostly chemicals and infectious agents) appear to have obvious implications in the pathogenesis of the disease, making it more prone in one area, and less prone in other areas.

More epidemiological studies should be conducted in the Eastern region to provide the true prevalence of PBC in the Eastern population. Furthermore, well-designed collaboration studies in different geographical areas that focus on risk factors in PBC patients are needed, in order to provide an idea on the factors that are influenced the most, and determine whether this is the same or different among patients from different regions. Finally, a large-scale study to identify the genes most susceptible to PBC is required to truly explore the unique risk carried by each population, combined with epigenetic studies that explore the relationship between these susceptible genes and the environmental factors that trigger these.

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Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

IDNW: study concept and design, gathering of references, drafting and revision of the manuscript, and supervision; CPS: drafting and revision of the manuscript.

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