Geoepidemiology of Autoimmune Liver Diseases

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Key Points

- The liver is a unique organ that plays a vital role in the defense against pathogens and the maintenance of tolerance against autoantigens.
- Despite its central role in immune tolerance, the liver, the largest lymphoid organ, is targeted by tissue-specific inflammatory responses in autoimmune liver diseases (AILD) including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC).
- The etiopathogenesis of AILD remains unclear but is multifactorial with genetic and environmental factors.
- Overlap syndromes with liver involvement in systemic autoimmune diseases are common and poorly understood or defined.
- AILD are relatively rare with wide geographic variations and aggregation in family members.
- The prevalence of AILD is low, but the health burden of these disorders is substantial.
- Considerable work needs to be done on both the genetic and environmental contributors to these diseases.

Introduction

The liver is a unique organ that plays a vital role in the defense against pathogens and the maintenance of tolerance against autoantigens [1]. As the largest lymphoid organ, the liver is targeted by tissue-specific inflammatory response, observed in primary autoimmune liver diseases (AILD) including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis), and primary sclerosing cholangitis (PSC). AILD is characterized by peculiar histopathological change and chronic course, progressively developing into cirrhosis or even malignancy. The etiopathogenesis of AILD remains unclear, but it is believed to be multifactorial with genetic and environmental factors involved. The clinical presentations vary in individuals and are usually atypical. In some cases, liver biopsy is required for the definite diagnosis. Of note, overlap syndromes and liver involvement of systemic autoimmune diseases also account for part of liver dysfunction in an autoimmune setting.

AILD is a relatively rare disease with geographic variations and aggregation in family members. Although the prevalence is low, the health burden of these disorders to both individuals and society is substantial. The incidence and prevalence are reported to be increased in AIH, PBC, and PSC during the past few decades. More and more attention has been paid to the AILD these years, and several population-based researches fill the vacancy of epidemiology of AILD. In this chapter, we are going to describe the epidemiological features of AILD and to discuss the impact of genetic and environmental factors on the development of these complex diseases.

Autoimmune Hepatitis

AIH is a chronic progressive inflammatory liver disease, clinically manifested as elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST), hyperglobulin-

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emia, and the presence of autoantibodies. If left untreated, AIH can lead to liver cirrhosis and hepatic failure, even hepatocellular carcinoma (HCC). The etiology of AIH is unclear, and it is hypothesized that unknown triggers result in autoimmune response to hepatocytes. Serologically, AIH can be divided into two subgroups: type 1 AIH which is characterized by antinuclear antibodies (ANAs) and/or anti-smooth muscle antibodies (ASMAs) and type 2 AIH which manifests anti-LKM-1 and anti-LC1. Exclusion of other liver disease and the correlation of clinical and histological presentations helps the diagnosis of AIH. The typical histologic features of AIH are interface hepatitis, emperipolesis, and hepatic rosette formation [2]. The treatment of AIH mainly depends on immunosuppressants, especially glucocorticoids and azathioprine.

AIH in the General Population

There is limited information regarding epidemiology on AIH. Previous population-based studies in Western countries revealed the annual incidence rates from 0.67 to 2.2/100,000 persons and a point prevalence from 11 to 26.9/100,000 persons [3–8]. The incidence and prevalence of AIH in Asia are relatively low, with an overall prevalence of 4–5.61 per 100,000 [9, 10]. AIH displays a female predominance (up to 95%), and most patients are middle-aged [4]. AIH may present at any age from childhood to elderly. Type 1 subtype of AIH mainly affects adults, while type 2 occurs frequently in younger patients. Type 1 AIH is more common than type 2 AIH, which is mostly a pediatric condition and more aggressive [11]. In Canada, the annual incidence of type 2 AIH is reported to be 0.23/100,000 children [12]. The 10-year cumulative mortality is estimated to be 26.4% in Northern Europe, at least twofold higher than the general population, especially patients with cirrhosis [5, 13]. Male gender and cirrhosis are associated with higher risk for HCC [14, 15]. Steroid treatment induces clinical, laboratory, and histological improvement in approximately 80% of patients [16], and the combination of steroids and azathioprine is associated with less side effects of steroids. However, a minority of patients will not respond to steroids and require alternative immunosuppressants such as mycophenolate mofetil.

Family Occurrence

Family occurrence has been rare. It has been reported that AIH accumulates in twins, siblings, parents, and children [17–19]. Recently, a Danish nationwide population-based study revealed that first-degree relatives of AIH patients have a fivefold increased likelihood to develop AIH, and the 10-year cumulative risk was 0.1% for the relatives [20]. Regarding the concordance of AIH in twins, no comprehensive studies have been reported previously. Nolte et al. described an acute hepatitis of unknown etiology, possibly with AIH origin in a monozygotic twin pair [18]. An epidemiological study in the Netherlands reported the concordance in monozygotic twins and discordance in dizygotic twins [17]. The Danish nationwide registry study also demonstrated a significantly higher risk of AIH in co-twins, and the probandwise concordance rate is higher in monozygotic than in dizygotic twins [20].

Risk Factors

Multiple factors contribute to the etiopathogenesis of AIH, including genetic predisposition (Table 11.1). Several genes have been reported to confer susceptibility to type 1 AIH, the strongest association of which is within the HLA-DRB1

Table 11.1 Main risk factors and comorbidities in AIH, PBC, and PSC

	AIH	PBC	PSC
Risk factors	HLA alleles	Genetic factors	Concomitant IBD, mainly UC
	Autoimmune polyendocrine syndrome type 1 with AIRE mutations	History of recurrent urinary tract infections	Continuous exposure to endogenous and exogenous toxins
	Environmental factors	First-degree relatives	Ischemic injury
	Intestinal dysbiosis	Past smoking	Bile toxicity
		Hormone replacement therapies	HLA alleles A1, B8, and DR3
		Frequent use of hair dye and nail polish	
		Pathogenic intestinal microbiota	
Comorbidities	PSC	Sjögren's syndrome	Ulcerative colitis
	Systemic autoimmune diseases such as SLE	Scleroderma	Colorectal and hepatobiliary malignancies
	IBD	Rheumatoid arthritis	
	Viral infections	Connective tissue disease	
		Autoimmune thyroiditis	
		Celiac disease	
		Increased risk of overall cancer	

locus, a class II MHC locus. In 2014, a genome-wide association study identified two relevant HLA alleles: HLA-DRB1*0301 as a primary susceptibility genotype and HLA-DRB1*0401 [21]. The study also demonstrated association between the AIH and variants of SH2B3 (rs3184504, 12q24) and CARD10 (rs6000782, 22q13.1) [21]. A number of other factors may trigger autoreactive response in AIH. The female predominance suggests a role for sexual hormones in AIH. Wei et al. demonstrated the dysbiosis in Chinese AIH population and identified several associated intestinal microbiota, suggesting the potential role of intestinal microbiome in the pathogenesis of AIH [22]. Administration of drugs could result in hepatic autoimmune responses. Drug-induced autoimmune hepatitis (DIAIH) is an increasingly recognized phenomenon, which has been reported to make up less than 10% of AIH case cohort in 2014 and increase to 18% in 2019 [8, 23, 24]. Notably, DIAIH differs from drug-induced liver injury by positive autoantibodies and response to immunosuppressants [24, 25]. Increasing usage of biological compound may contribute to the growing number of DIAIH.

Comorbidities

Some diseases have been reported to be associated with AIH, including systemic autoimmune diseases (i.e., systemic lupus syndrome, multiple sclerosis) [26], inflammatory bowel diseases (IBD) [27], celiac disease [28], and viral infections (i.e., hepatitis C virus (HCV), Epstein-Barr virus (EBV)) [29]. A subgroup of patients manifest signs of both AIH and PSC, named as autoimmune sclerosing cholangitis (ASC). Notably, IBD is a common comorbidity in ASC patients, the prevalence of which closely mirroring that in PSC patients in a population-based study [30]. The coexistence of AIH and IBD ranges from 4.5% to 18%, less common than that in ASC patients [31, 32]. AIH is also prevalent in HCV patients, in which the viral antigen is a mimicry of smooth muscle [33]. Thus, a mechanism of molecular mimicry is implicated in AIH patients with HCV infection. In addition, AIH patients have a higher risk to develop osteopenia secondary to prolonged usage of steroids as well as metabolic syndrome. Hematopoietic risks also increase as the side effects of azathioprine.

Primary Biliary Cholangitis

PBC is a chronic cholestatic liver disease characterized by nonsuppurative destructive inflammation of small and medium-sized bile ducts. Intrahepatic cholestasis and peribiliary fibrosis can culminate over time in an end-stage cirrhosis, eventually resulting in HCC. The majority of PBC cases arise insidiously, and the diagnosis is based on the presence of serum autoantibodies and the elevation of cholestatic enzymes (i.e., alkaline phosphatase, gamma-glutamyltransferase) [34]. Anti-mitochondrial antibody (AMA) reactive against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) is a specific serum marker in PBC. Serum antinuclear antibodies (ANAs), such as anti-gp210 and anti-Sp100, are accepted as PBC-specific markers during diagnosis. Liver biopsy is unnecessary unless either serum autoantibodies or elevation of cholestatic enzymes is absent. The pathogenesis of PBC remains obscure, but the detection of autoreactive T cells and autoantibodies suggests autoimmune humoral responses against mitochondria [35, 36]. Ursodeoxycholic acid (UDCA) is the first-line therapy, and obeticholic acid (OCA) is optional for those UDCA-unresponsive or non-tolerant cases.

PBC in the General Population

The incidence and prevalence of PBC vary widely in different regions and seem to be increasing over time (Table 11.2). In 2012, systemic review of epidemiological studies worldwide reported that the incidence rate ranges between 0.9 and 5.8 per 100,000 inhabitants, with 92% of female patients, and the prevalence of PBC ranges from 1.91 to 40.2 per 100,000 inhabitants [37]. A recent meta-analysis of epidemi-

Table 11.2 Incidence and prevalence rates reported for PBC

P	Country/region	Incidence (per 100,000)	Prevalence (per 100,000)
1980	UK	5.8	54
1980	UK	10.6	40.2
1983	UK	10	37–144
1984	Sweden	4–24	28–92
1984	Western Europe	4	23
1985	Sweden	14	128
1987	UK	11–15	70–93
1990	Sweden	13.3	151
1990	Canada	3.26	22.4
1990	Northern England	19	129–154
1995	Australia	N/A	19.1
1995	Estonia	2.27	26.9
1997	UK	14–32	240
2000	USA	27	402
2004	Australia	N/A	51
2005	Spain	17	195
2009	Canada	30	227
2012	Southern Israel	20	238
2012	Iceland	22.5	383
2016	South Korea	8.75	47.5
2017	Hong Kong	8.4	56.4
2019	Japan	N/A	33.8

N/A not available
Adapted from [37] and [38]

ology of PBC in the Asia-Pacific region demonstrated a pooled overall incidence as 8.55 per 100,000 people. The pooled overall prevalence was estimated to be 118.75 per 100,000 people with a respective pooled prevalence of 36.24 and 146.47 cases per 100,000 during pre-UDCA era and post-UDCA era [38]. Of note, large population-based study reported the incidence and prevalence rates increase over time with a mean annual incidence of 1.1 between 2000 and 2007. It stated that the net growth of PBC patients in the Netherlands was attributed to increase in incidence instead of decrease in the number of deaths [39]. Another study in Sweden mentioned an increased prevalence of PBC during 30 years although incidence remained stable [40]. It is worth mentioning that countries, ethnicity, and variable criteria for case inclusions may explain the wide range of incidence and prevalence rates between different countries. However, the increase in prevalence may probably attribute to the increased recognition, better data capture, improved laboratory detection methods, and increased survival after UDCA treatment.

PBC has a female predominance with a female to male ratio of about 10 to 1 [34]. A cohort study in the USA estimated 12-year prevalence of PBC with a highest adjusted prevalence value among women (42.8 per 100,000) [41]. The symptoms are similar in men and women, but men may have a worse disease progression with a higher risk to develop HCC. PBC is closely associated with a higher risk of HCC [42]. Male sex and advanced liver stage are independent risk factors for the development of HCC in patients with PBC, suggested by the representative cohort in China and Japan [43, 44].

An international meta-analysis in Western countries reported that the 5-year, 10-year, and 15-year transplant-free survival rates were 90%, 77.5%, and 65.6%, respectively [45]. The 5-year death/liver transplantation in PBC patients is 4.02% in the Asia-Pacific region [38]. Before the availability of UDCA, PBC patients usually develop to an advanced stage with a subsequent median survival of 6–8 years [34]. In the UDCA era, the introduction of UDCA at early stage improves the survival rate of PBC patients [46–48]. The survival rate of patients who respond to UDCA treatment is similar to that of an age-matched and sex-matched healthy people [46]. The favorable effects of UDCA are probably attributed to the delay of histological progression and the development of esophageal varices.

Family Occurrence

The studies of familial PBC revealed a fundamental role played by genetic factors and environmental influences on the pathogenesis of PBC. The first-degree relatives of PBC patients have a higher risk of developing PBC [49]. A recent nationwide study with genealogical database has defined the relative risk of the first-, second-, and third-degree relatives of PBC patients as 9.13, 3.16, and 2.59, respectively. The fourth- and fifth-degree relatives also had a slight increase in the relative risk [50]. Apart from the familial aggregation of occurrence, the AMA aggregate among first-degree relatives as well, which recommends a close follow-up of these relatives for early diagnosis [51]. However, in AMA-negative first-degree relatives and AMA-positive first-degree relatives with normal alkaline phosphatase levels at initial assessment, the risk of developing PBC in the subsequent 8 years is low [52]. A recommendation for a standardized follow-up approach for family members of PBC patients requires further investigation. By comparing eight monozygotic and eight dizygotic twin pairs, concordance rate for PBC is estimated to be 63% in monozygotic twins and null in dizygotic twins [53]. Of note, the monozygotic concordance rate is the highest reported for autoimmune disease. However, the sibling relative risk, namely, the odds ratio for PBC of an individual with a sibling affected by PBC, is 10.5 among the lowest for autoimmune disease. Genome-wide analysis of epigenetics in monozygotic twins and sisters discordant for PBC has revealed particular differences in DNA methylation profiles, copy number variation, and gene expression which explains the different phenotypes in siblings [54].

Risk Factors

Although the etiopathogenesis of PBC remains to be determined, several risk factors have been identified (see Table 11.1). The familial occurrence suggests the genetic predisposition of PBC, like many other autoimmune diseases. HLA class II alleles are believed to be associated with the development of PBC, especially HLA-DRB1*08 allele family [55]. In recent years, high-throughput technologies such as genome-wide association studies (GWAS) have revealed more risk loci associated with PBC. Forty non-HLA alleles possibly contributing to PBC susceptibility are discovered according to the GWAS analyses from different countries. Even though it differs among different studies and populations, the identified genes participate in certain pathways including antigen presentation and production of interleukin (IL)-12 (i.e., IRF5, SOCS1, IL-12A, etc.), activation of T cells and interferon (IFN)-γ secretion (i.e., IL12R, TYK2, STAT4, etc.), and activation of B cells and production of immunoglobulins (i.e., ARID3a, POU2AF1, IKZF3, etc.) [56–58].

The environmental factors including urinary tract infections, cigarette smoking, and the use of hormone replacement therapies are associated with increased risk of PBC [59]. A strong relationship lies between smoking and PBC, demonstrated by studies from the UK and France [60, 61]. Molecular mimicry is considered to be the underlying mechanism by which pathogens and xenobiotics trigger autoim-

mune responses [62]. It is well established that humoral and cellular autoimmune responses in PBC are associated with pyruvate dehydrogenase complex (PDC-E2). The homozygous enzyme of PDC-E2 in microbiota or chemical xenobiotics can induce serological and histopathological changes in PBC [63]. Recent studies have revealed a correlation between the intestinal microbiome and PBC, suggesting the potential risk of dysbiosis in the pathogenesis of PBC [64].

Comorbidities

PBC frequently coexists with rheumatic disorders in up to 30% of cases. A monocentric study demonstrated the co-occurrence in 61.2% of cases of PBC patients, with the most common comorbidity as Sjögren's syndrome, followed by Raynaud's phenomenon and Hashimoto thyroiditis [65]. Other extrahepatic autoimmune diseases that might occur include Graves' thyroiditis, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, vasculitis, and celiac disease [65, 66]. Interestingly, extrahepatic autoimmune diseases commonly coexisted with PBC have a tendency to be less severe. For example, systemic sclerosis (SS) most commonly associated with PBC is limited to cutaneous tissue, and the disease progression is much slower compared with matched patients with PBC alone [67–69]. Similar to other chronic liver diseases, PBC is associated with a higher risk of HCC. The risk of HCC is reported higher in PBC, ranging from 6 to 18.8 times that of general population [42, 70, 71]. An internationally representative cohort study has reported that the incidence of PBC-HCC is significantly greater in male, patients with advanced disease, and 12-month UDCA non-responders [72]. Osteoporosis with an increased fracture risk is frequently encountered in PBC patients, largely driven by deficient bone formation [73–75]. Thus, vitamin D and calcium supplementation should be addressed in the clinical management of PBC patients.

Primary Sclerosing Cholangitis

PSC is a complex chronic cholestatic autoimmune disease with unknown causes. Unlike PBC, PSC is characterized by fibrotic obstructive cholangitis involving intra-/extrahepatic bile ducts and forms "onion-skin" fibrosis. Classically, PSC affects large bile duct while some may involve small ducts or overlap AIH. In a retraspective study, 89.9% patients had classical or large duct disease [76]. PSC is often associated with IBD, suggesting the important role of gut-liver axis in the pathogenesis of PSC. The recent guidelines for PSC suggest that all patients with IBD should receive an assessment for PSC [77]. The diagnosis is mainly based on abnormal cholestatic enzymes and distinctive radiological manifestations: segmental stenosis and dilation in magnetic resonance imaging (MRI). Liver biopsy is unnecessary unless in the case of small-duct PSC. There is no effective medical therapy for PSC, and many patients progress to end-stage liver disease that requires liver transplantation (LT) or even cholangiocarcinoma (CCA). PSC patients usually have a higher risk of developing CCA, and the annual incidence of developing CCA ranges between 0.5% and 1.5%, and the lifetime risk is between 6% and 12% [78].

PSC in the General Population

The epidemiological information of PSC is poorly described. The incidence rate of PSC ranges from 0.07 to 1.3 per 100,000 inhabitants per year, and the prevalence ranges from 0.22 to 16.2 (Table 11.3) [79]. A meta-analysis in 2011 reported a pooled incidence rate of 1.0 (0.82–1.17) per 100,000 person-years in six population-based studies in western countries. The pooled incidence rate ratio for males versus females was 1.7 (1.34–2.07), correlating with the susceptibility of males [80]. The incidence of PSC seems to be higher in Northern Europe and Northern America, but relatively low in Asia and Africa. The widely variable incidence and prevalence might be attributed to the ethnical diversity, and genetic background may play a role in the etiology and natural history of PSC [81]. Besides the genetic background, the study design and the inclusion criteria may partly explain the differences. A recent retrospective cohort study in the UK revealed an incidence of 0.68 per 100,000 person-years and a prevalence of 5.58 per 100,000 person-years, which is the highest incidence and prevalence reported ever in the UK [82]. It has been proposed that the incidence of PSC is increasing. Two cohort studies revealed a significant increase

Table 11.3 Incidence and prevalence rates reported for PSC

Year	Country/region	Incidence (per 100,000)	Prevalence (per 100,000)
1994	Spain	0.07	0.22
1996	Canada	N/A	6.5
1998	Norway	0.7	5.6
1998	Norway	N/A	6.5
2002	Singapore	N/A	1.3
2003	USA	0.9	13.6
2004	UK	0.91	12.7
2007	Canada	0.92	N/A
2008	UK	0.41	3.85
2010	Sweden	1.22	16.2
2011	USA	0.41	4.15
2013	Netherlands	0.5	6
2008, 2016	Japan	N/A	0.95
2019	Japan	N/A	1.8

N/A not available
Adapted from [146]

in incidence ratio of PSC over time with an average annual percent change of 3.06 in one study [83, 84]. A questionnaire-based survey conducted in Japan reported the point prevalence of PSC was 1.8 in 2016, indicating an increasing trend compared to the prevalence of 0.75 in 2007 [85]. Most patients with PSC have serum antibodies such as ANA, anti-SMA, and antineutrophil cytoplasmic antibody (ANCA) but are not specific. Recent studies identified zymogen granule glycoprotein 2 (GP2) as the first autoimmune mucosal target in PSC, the detection of antibody against which could be used for risk stratification [86]. Contrary to PBC, PSC has a male predominance, with a male/female ratio of 2/1 [87]. Female patients are usually associated with a lower risk of LT or death or malignancies [76]. The median transplant-free survival time of PSC is 14.5 according to an international retrospective study. The occurrence of hepatopancreatobiliary malignancies, mainly CCA, is associated with a significantly increased risk of patient mortality [76].

Family Occurrence

Unlike PBC, data on family occurrence of PSC is limited. A case report in 2005 described two brothers diagnosed with PSC who were positive for the susceptibility HLA haplotypes DR3-DQ2 and DR6-DQ6, suggesting a genetic origin of PSC [88]. In a monocentric study in Sweden, first-degree relatives of PSC patients have a PSC prevalence of 0.7%, nearly 100-fold increased risk compared to that of general population, indicating a potential role of genetic disposition [89]. Another study from Sweden also confirmed an increased risk of PSC in first-degree relatives of PSC patients. The offspring, siblings, and parents of PSC patient cohort had a significantly higher risk of cholangitis with the hazard ratios and 95% confidence intervals, 11.5 (1.6–84.4), 11.1 (3.3–37.8), and 2.3 (0.9–6.1), respectively [89].

Risk Factors

The etiology of PSC is unclear, but several genetic and non-genetic predispositions have been identified (see Table 11.1). Early serological studies documented the association between HLA complex and PSC. The following GWAS confirmed the importance of HLA as a risk locus. HLA-B*08 and DRB*03 have a strong association with PSC, with an odds ratio of 4.9 and 3.8, respectively [90]. Recently, the largest GWAS of PSC has identified a new significant locus which affects the expression of UBASH3A, a gene involved in the regulation of T cell signaling [91]. As for the genetic contribution to the disease severity and progression, genetic variant rs853974 outside the HLA complex is reported to be relevant to the disease progression of PSC [92]. In accordance with the strong association between PSC and IBD, PSC shares some susceptibility loci with PSC. However, most of these loci have failed to show a genetic link to PSC, suggesting that PSC-IBD might be a unique phenotype. As for environmental factors, smoking is considered to be a protective factor for PSC, independent of its protective effects on UC [93]. Like PBC and AIH, dysbiosis occurs in PSC patients, including bacteria and fungi [94, 95]. The identification of PSC marker genera either relevant to intestinal inflammation severity or biliary obstruction also suggests the association between PSC and microbiome [96].

Comorbidities

As mentioned above, PSC has a strong correlation with IBD, mostly ulcerative colitis (UC). The comorbidity of Crohn's disease (CD) is less common than UC, and PSC patients usually show milder symptoms in the setting of CD than UC [76, 97]. Approximately 75% of PSC patients have concomitant IBD, while the prevalence of PSC is 8.1% in IBD patients [98, 99]. More and more studies demonstrated that IBD patients associated with PSC are identical to patients with IBD alone with a relatively mild clinical course but an increased risk of developing colorectal carcinoma [100, 101]. The presence of PSC symptoms at PSC diagnosis in IBD patients is the only factor related with this increased risk of colorectal carcinoma [102]. Whether PSC coexisting with IBD differs from PSC alone remains unclear and requires further investigation. CCA is another common comorbidity in PSC with a 398-fold increased risk of developing CCA in PSC patients compared to the general population in a population-based multicenter study [84]. And the risk of CCA is significantly higher in patients with concomitant IBD and PSC than general population in a clinical study with 20-year follow-up [103].

Overlap Syndromes

Coexistence of clinical features of at least two different AILDs is defined as overlap syndromes. In overlap syndromes, shared clinical, immunological, and histological features exist between AIH, PBC, and PSC. In most cases, overlap syndromes are between AIH and PBC or AIH and PSC, but a few cases have reported the overlap syndrome of PBC and PSC [104–106]. The epidemiological information of overlap syndromes is limited due to the diagnosis and publication bias.

AIH-PBC overlap syndrome is more common than AIH-PSC, largely due to the relative frequent occurrence of PBC and AIH in the spectrum of AILDs. The prevalence of AIH-PBC overlap syndrome is estimated to be 4.3–9.2% among patients with PBC and 2–19% among patients with AIH [107, 108]. The adjusted prevalence of AIH-PBC overlap

syndrome by eliminating score for female gender or the presence of other autoimmune disorders is 4% [109]. AIH-PBC overlap syndrome seems to aggregate in Hispanic patients, with a significantly higher prevalence to develop overlap syndrome than that of non-Hispanic patients (31% vs. 13%, respectively) [110]. The frequency of cirrhosis and cirrhotic complications (i.e., gastrointestinal bleeding, portal hypertension, esophageal varices, etc.) are reported significantly higher in the overlap group than PBC alone [111]. A recent study compared the natural history of patients with PBC alone to those with overlap syndrome, and a decreased 5-year adverse event-free survival was observed in overlap patients [112]. The treatment of AIH-PBC overlap depends on the combination of steroids and UDCA, more effective than UDCA monotherapy according to a meta-analysis [113].

AIH-PSC overlap syndrome is a rare syndrome that has been described in both children and adults. AIH-PSC overlap is more common in children, adolescents, and young adults. The diagnosis is made upon the overt cholangiographic or histologic findings of PSC together with robust histologic features of AIH [108, 114]. The prevalence of characteristic cholangiographic appearance suggesting PSC found in adult AIH patients varies between different studies, ranging from 2% to 10% [115, 116]. The prevalence to develop PSC is much higher in children with AIH, up to 50% [31]. AIH is rarely diagnosed in patients with an original diagnosis of PSC, the prevalence of which ranges from 7% to 14% [117, 118]. The adverse outcome-free survival of patients with PSC/AIH overlap syndrome is reduced [119]. Interestingly, AIH-PSC overlap patients seem to have a better outcome than straightforward PSC patients with the combination treatment of UDCA and immunosuppressants [120, 121]. AIH-PSC overlap patients are still regarded to have a poorer prognosis than patients with classical AIH and AIH-PBC overlap [122].

Liver Involvement in Systemic Rheumatic Diseases

Liver involvement in systemic rheumatic diseases is common even though the liver is not a common target organ. The epidemiology of these liver autoimmune conditions is largely correlated to the prevalence of systemic rheumatic diseases and the susceptibility of liver involvement. Several common conditions will be discussed in detail in the following part.

IgG4-Related Diseases

IgG4-related disease is a systemic inflammatory condition that can affect multiple organs. Involvement of nearly every anatomic site has been reported, but the most commonly affected organs are pancreas, biliary tract, major salivary glands, lacrimal glands, retroperitoneum, and lymph nodes [123]. IgG4-related diseases share similar histological appearances: lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis with variable presence of eosinophils [124, 125]. With regard to IgG4-related hepatobiliary disease, characteristic imaging features of segmental or diffuse biliary strictures with thickened bile duct walls are required to support the diagnosis apart from histopathological features [126]. The prevalence of IgG4-related hepatobiliary disease remains unclear. A nationwide survey in Japan identified 43 IgG4 sclerosing cholangitis (IgG4-SC) without autoimmune pancreatitis (AIP). The male to female ratio was 3.3 to 1 in IgG4-SC with an average age of onset of 69.3 years [127]. A novel concept of IgG4-realted AIH has been proposed [128, 129]. Patients who met the diagnostic criteria for AIH had a high serum IgG4 level, and abundant IgG4-positive plasma cells were reported to be diagnosed as IgG4-related AIH. The prevalence of IgG4-SC and IgG4-AIH is lacking due to the scarce reports.

Sarcoidosis

Sarcoidosis is a chronic granulomatous inflammatory disease that can affect any organ. Liver involvement is relatively common in sarcoidosis with prevalence ranging from 5% to 30% [130]. It has been found that 50–65% of sarcoid patients have hepatic involvement as per liver biopsy [131]. A population-based study reported a prevalence of 6%, and cholestatic enzymes are elevated in the majority of patients [132]. A close association has been demonstrated between sarcoidosis and hepatitis C virus infection [133]. It has also been reported that a link lies between sarcoidosis and PBC or AIH [32, 134]. The histological abnormalities of hepatic sarcoidosis include non-caseating granulomas, intrahepatic cholestasis, periportal fibrosis, etc. For patients with end-stage hepatic sarcoidosis who require liver transplantation, the 10-year survival rate is estimated to be 51.3%, lower than matched PSC/PBC group (61.5%) in a monocentric study [135].

Connective Tissue Diseases

Connective tissue diseases (CTDs) are composed of a large and heterogeneous group of immunological disorders with unknown etiology. Liver, as the largest lymphoid organ, is frequently involved in CTDs in the form of abnormal biochemical indexes.

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that can cause damage to almost every organ. It has been reported that patients with SLE have a 9.3–59.7% chance to develop liver dysfunction during follow-up [136, 137]. With the criteria of liver disease as two-fold elevation of liver enzymes, a monocentric study revealed

20.7% of SLE patients have liver disease and the prevalence to develop liver dysfunction is increased in males, indicating that male patients with SLE are more susceptible to liver involvement [138]. SLE-associated hepatitis, termed lupus hepatitis, occasionally occurs. It has been reported that 4.7% of SLE patients develop AIH and 19.4% of SLE patients have liver enzyme abnormalities [139].

Sjögren's syndrome (SS) mainly affects salivary and lacrimal glands, manifested by keratoconjunctivitis sicca, xerostomia, and swelling of salivary glands. Liver involvement is commonly seen in SS. About 27–49% of SS patients have abnormal liver function with 11–21% found to develop hepatomegaly [140]. Of note, a group of SS patients have positive serum AMA [141]. AMA is considered to be associated with pathogenesis of SS. In both PBC and SS, the autoantibodies can target bile duct and salivary gland, partly explaining the presence of AMA in SS patients. SS patients have a higher risk of developing AILD with 9% PBC and 4% AIH [142, 143]. It is worth mentioning that liver function assessment should be conducted in SS patients regularly.

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by joint involvement and extra-articular manifestations. Liver involvement is not a typical extra-articular manifestation in RA. The presentation of liver damage in RA is a cholestatic pattern with predominantly elevated ALkaline Phosphatase (ALP) and gamma-Glutamyl Transpeptidase (γGT). Abnormal liver function test results are present in between 18% and 50% of cases [144]. A recent cross-sectional study identified 44% liver involvement in RA patients with most of the cases asymptomatic [145]. Notably, the liver involvement in RA may be attributed to the hepatotoxicity of medications.

Besides the CTD mentioned above, systemic sclerosis, myopathies, antiphospholipid syndrome, and many other systemic autoimmune diseases can involve liver, characterized by abnormal liver enzymes or hepatomegaly. The prevalence of liver damage caused by systemic autoimmune disease varies between different diseases and ethnic groups. Liver function should be well-monitored once the diagnosis of CTD is made.

Conclusion

The increased annual incidence and prevalence have been drawing attention to the management of AILDs during the past decades. AIH, PBC, PSC, and overlap syndromes are the most recognized ones that affect liver in situ. Liver involvement of systemic rheumatic diseases usually does not display specific biochemical nor histological features. Although the prevalence is increasing, AILDs remains rare. The epidemiological features of these kinds of diseases are limited. Most AILDs have a female predominance with the exception of PSC and IgG4-related diseases. Ethnic and sexual factors usually play an important role in the occurrence and pathogenesis. Genetic predisposition is considered to have a strong association with the onset of AILDs. The management of these kinds of diseases usually relies on immunosuppressants, including glucocorticoids and immunosuppressive drugs. To sum up, AILDs should be considered in patients with liver dysfunction when the infectious and metabolic causes are ruled out.

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