



Geoepidemiology of autoimmune liver diseases

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Autoimmune liver diseases are characterized by immune mediated injury of bile ducts or hepatocytes, thus including cholangiopathies such as primary biliary cirrhosis, primary sclerosing cholangitis, and immunoglobulin G4-associated cholangitis, and autoimmune hepatitis. Although the liver was one of the earliest recognized sites of autoimmune aggression, the aetiology of autoimmune liver diseases remains largely obscure and their clinical management still difficult. Since an ever increasing applicability of immunology to a wide variety of chronic diseases, basic and clinical knowledge on autoimmune liver diseases grow rapidly in the last few years. This review will mainly focus on the available geoepidemiology data of these disorders, but it will deal also on their main clinical characteristics, as well as mechanisms of etiopathogenesis, for each of the above diseases, together with their overlap forms. In particular, we will discuss the major underlying immunomolecular mechanisms of development, the genetic influences, the growing number of immuno-serological diagnostic markers, and the increasingly effective therapeutic possibilities.

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1. Introduction

Autoimmune diseases were recognized during the 1950s as novel pathogenetic entities in both humans and animals, and today there are about 80 different conditions due to autoimmunity. Among them, the autoimmune liver diseases (ALD) were the earliest recognized sites of autoimmune diseases [1]. From that time, clinical awareness of ALD has increased, our knowledge of etiopathogenesis has become more precise, novel laboratory biomarkers and more effective therapies available. Although the low prevalence of ALD, the health burden of these disorders is still very substantial. Indeed, ALD may affect children, individuals at highly productive stages of adult life, as well as in later years. In addition, ALD are life-long, and often cause distressing symptoms and complications, or side-effects of therapy. In this chapter the basic knowledge and the most recent advances on ALD will be critically described, with a particular focus on the geoepidemiology aspects of ALD and the role of environmental factors in these disorders. Indeed, epidemiologic studies may help to determine the impact of the environment on the development of complex diseases.

ALD are classified into two main entities according to the target cell of immune injury, i.e. hepatocyte and cholangiocyte. While autoimmune hepatitis (AIH) is a more uniform condition, the autoimmune cholangiopathies comprehends disorders of the intra-hepatic (primary biliary cirrhosis, PBC) and extra-hepatic (primary sclerosing cholangitis, PSC, and immunoglobulin G4-associated cholangitis, IAC) biliary ducts (Table 1) [2,3]. While AIH and PBC are prototypic autoimmune diseases, the inclusion of PSC among the autoimmune diseases is still controversial since criteria are only in part fulfilled thus it should be considered an immuno-related disorder. Although IAC is a novel and largely unknown condition, its steroid-responsiveness strongly suggests an autoimmune origin. The possibility that hepatocytes and cholangiocytes can undergo simultaneous injury has led to the nomination of different “overlap syndromes” involving AIH [4].

It is accepted that pathogenesis of ALD is multifactorial, with environmental and genetic factors interplaying to determine disease onset and progression [5–9], although the quantification of environmental influences is very difficult [10,11]. The predisposition to many ALD represents the net effect of protective and enhancing genes, although no specific genes have yet been identified.

The diagnosis of ALD requires the exclusion of other causes of liver damage, such as viral, toxic, alcoholic, genetic, metabolic or non-alcoholic fatty liver disease, and the evaluation of clinical, biochemical, histopathological, and cholangiographic features specific to each of the ALD conditions. Although most of the criteria have limited sensitivity and specificity, combinations of diagnostic

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Table 1

Distinctive features of autoimmune liver diseases.

	AIH	PBC	PSC	IAC
Bile duct involvement	No	Small-size	Small-large size	Small-large size
Bacterial cholangitis	No	No	Yes	?
IBD	No	No	Yes	No
AMA	Negative	Positive	Negative	Negative
LKM-1	Positive (type 2)	Negative	Negative	Negative
Immunoglobulin levels	↑↑↑	Normal	Normal	Normal
IgM levels	↑	↑↑↑	Normal	Normal
IgG4	Normal	Normal	Normal	↑↑↑
Transaminases levels	↑↑↑	↑ (stable)	↑ (fluctuating)	↑
AP and GGT levels	↑	↑↑↑ (stable)	↑↑↑ (fluctuating)	↑↑↑
Ursodeoxycholic acid	No	Yes	Yes (?)	No
Steroid/immunosuppressive	Yes	No	No	Yes

Abbreviations: AIH: autoimmune hepatitis; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; IAC: Immunoglobulin G4-associated cholangitis; IBD: inflammatory bowel diseases; AMA: anti-mitochondrial antibodies; LKM-1: anti-liver kidney microsome type 1; AP: Alkaline phosphatase; GGT: gamma-glutamyltranspeptidase.

features have high sensitivity and specificity [2,3]. It is to note that with the increasing precision in diagnosing ALD, an increasing numbers of overlap cases are reported [4]. Serum autoantibodies has a major diagnostic role, and may also allow to identify subsets of patients with different prognosis [12]. The continuing efforts in understanding their molecular definition allowed to improve their diagnostic and prognostic utility in clinical practice.

Clinical presentations of ALD changed over time compared with earlier days and both AIH and PBC are responsive to standardized treatment regimens; although ursodeoxycholic acid (UDCA) in PBC has undoubted therapeutic benefits, some patients will still require a liver transplant for eventual end-stage disease; A for many other diseases, also for ALD post-transplant morbidity and mortality are largely reduced. Concerning transplantation, the complications of graft-versus-host disease and allograft rejection still exist but are now largely manageable.

2. Autoimmune hepatitis

AIH is a progressive, inflammatory disease of the liver, occurring mainly in females, both in children and adults, and characterized by elevated serum transaminase and immunoglobulin G (IgG) levels, positive organ and non-organ specific autoantibodies, and a histological picture of interface hepatitis [3,13] (Table 1). Based on serology, two types of AIH can be recognized: type 1 AIH, positive for anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibodies; type 2 AIH with anti-liver kidney microsomal type 1 (LKM-1) antibody (Table 2). The disease was first described as a form of chronic

Table 2

Classification of autoimmune hepatitis.

Type 1	Serum Autoantibodies Anti-nuclear antibody (ANA) Smooth muscle antibody (SMA) Anti-actin antibody (AAA) Anti-soluble liver antigen/liver-pancreas antigen (SLA/LP) Atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) Anti-mitochondrial antibody (AMA)
Type 2	Anti-liver/kidney microsome-1 (LKM-1) Anti-liver cytosol-1 (LC-1)

hepatitis in young women by Waldenström in 1950 [14], and the estimated point prevalence of type 1 (Type 1 AIH is the most common form worldwide, constituting at least 80% of cases) was about 5–10 per 100,000 population. The aetiology of AIH is largely unknown, though both environmental and genetic factors seem to be involved in its development and progression [15]. Immune mediated aggression against host liver antigens are believed to be the major pathogenic mechanism.

2.1. Geoepidemiology

Few data are available on the prevalence and the incidence of AIH. Indeed, most of the information regarding AIH comes from studies of chronic active hepatitis and performed before the introduction of the Autoimmune Hepatitis Group Scoring System, that is of a standardized way of evaluating patients. In addition, hepatitis C were not excluded. In Norway, the annual incidence was 1.9 cases of AIH per 100,000 with a prevalence of 17 cases per 100,000 population [16]. Similar findings were more recently reported in Spain, with an annual incidence of 0.8 cases of AIH per 100,000 and a prevalence of 11.6 cases per 100,000 population [17].

2.2. Etiopathogenesis

As for other autoimmune disorders, AIH is considered a 'complex trait' disease. Indeed, it is believed that the mode of inheritance of AIH involves more than one gene operating in concert to reduce or to increase the risk of disease [15,18]. The major histocompatibility complex (MHC) is one of the most extensively studied regions in AIH [19,20]. Although the precise role of the various associated MHC alleles is generally unclear, it is believed that specific alleles enhance the autoimmune response by enhancing immunogenicity and the expressed repertoire of T cells [21]. The HLA-DRB1*0301 and HLA-DRB1*0401 alleles have been found to be associated with AIH [20]. In addition, in Japan, Mexico and Argentina, AIH susceptibility is linked to DRB1*0405 and DRB1*0404, while in South America the HLA DRB1*1301 allele is associated to pediatric type 1 AIH and is also associated with infections such as hepatitis A virus [22]. Potential role of other genetic polymorphisms was also suggested but remains under investigation [20,23]. No genome-wide studies have yet to be performed in patients with AIH [18]. Overall, as in other ALD, the identification of AIH-causing genetic variants is difficult for several reasons, such as inadequate study designs, methods for recruitment of case and controls, and the extensive linkage disequilibrium and variability among the MHC alleles [18].

Although the autoantigens that trigger the autoimmune aggression in AIH are still unknown, the recent identification of anti-soluble liver antigen/liver-pancreas (anti-SLA/LP) autoantibodies and the cloning and characterization of the SLA/LP antigen, suggested that a 50-kD cytosolic protein is a major antigen at least in a subset of patients affected by type 1 AIH [24]. Much more is known about the autoimmune mechanism in type 2 AIH. Indeed, the presence of B-cell epitopes of cytochrome P-450 2D6 (CYP2D6) and the cross-reactivity with different virus homologues strongly suggest that relevant antigens is located within CYP2D6 [25]. Finally, recent elegant studies by Longhi and colleagues on the role of CD4+ regulatory T cells have suggested the concept that failure of or escape from normal suppression of immunoreactivity against self antigens plays a key role in the development of autoimmunity [15]. This issue is of great relevance for the possible therapeutic implications [26].

In the past several attempts have been made to develop a reliable animal model that reflects the chronic hepatic destruction that occurs in humans affected by AIH [27]. However, only recently it

has been demonstrated for the first time that infection with a virus expressing a natural human autoantigen breaks tolerance, resulting in a persistent form of severe, autoimmune liver damage [28,29].

2.3. Histology

The histologic features of AIH resembles that of chronic hepatitis with no findings specific to the disease. The inflammatory component is mainly characterized by a mononuclear cell infiltrate which invades the hepatocyte boundary (limiting plate) and infiltrates the surrounding parenchyma (piecemeal necrosis). Often include eosinophils and plasma cells, and the portal lesion generally spares the biliary tree. Fibrosis is generally present in all the forms of AIH but it is extensive only in advanced disease. In a subsets of AIH patients with a pharmacologically-induced or spontaneous remission, histologic changes may revert to normal [30].

2.4. Classification, diagnosis, and clinical features

The widely accepted classification of AIH is based on patterns of circulating antibodies (Table 1) [3,31,32]. Type 1 AIH is frequently characterized by ANA, SMA, and anti-actin antibody (AAA). The identification of other circulating autoantibodies can be found, such as anti-SLA/LP and atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) but their diagnostic role is generally weak. Anti-SLA/LP is the most specific autoantibody in type 1 AIH but it is present in only one-third of patients affected by type 1 AIH. On the contrary, atypical pANCA is non-specific, but often detected. LKM-1 and anti-liver cytosol-1 (LC-1) antibodies characterize type 2 AIH.

The diagnosis of AIH is based on characteristic biochemical and clinical findings, serum autoantibodies, increased levels of serum immunoglobulins, and a compatible histologic picture. In order to standardize diagnosis, a scoring system was proposed by the International Autoimmune Hepatitis Group [13]. However, being often problematic, a simplified and more accurate system for wider application in clinical practice was more recently developed [33].

Although there is a female predominance, AIH can occur in children and adults of both sexes [34]. Type 2 AIH affects predominantly children and young women, and is rare North America [35]. Although AIH was thought to be primarily a disease of the young and middle aged, it is now clear that it frequently occurs in the elderly [36]. AIH is characterized by a marked variability in clinical manifestations, ranging from an asymptomatic presentation to a fulminant hepatic failure [3,13]. AIH patients can have an occult disease which may progress to advanced stage and present only with signs of liver decompensation while, on the contrary, it is to note that subclinical disease may also ensue for long periods after presentation.

2.5. Treatment

It is important to note that an appropriate management of AIH can reduce inflammation, slow disease progression, and prolong survival [13]. However, about one-third of patients with AIH need of other than standard treatment. Standard medications for initial and maintenance regimens are prednisone (or prednisolone) alone or in combination with azathioprine (or 6-mercaptopurine) (Table 1). In children, standard treatment consists of prednisolone 2 mg/kg/day (maximum 60 mg/day), and then maintained on the minimal dose able to sustain normal transaminase levels, usually 2.5 mg/day or 5 mg/day depending on the age [37]. Azathioprine can be added at a dose of 0.5–2.5 mg/kg/day. Particular attention should be paid to azathioprine toxicity which can be predicted by genotyping thiopurine methyltransferase (the gene catalyzing the methylation of 6-mercaptopurine and 6-thioguanosine 5'-

monophosphate) and/or by measuring circulating levels of 6-mercaptopurine metabolites [38]. The majority of patients with AIH requires life-long maintenance therapy, and although no guidelines exist for decisions regarding withdrawal of medications, aminotransferase levels $<2\times$ normal are generally consider to reduce medications [39]. The roles of cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate, cyclophosphamide, UDCA, budesonide and other immunosuppressive medications are still under investigation [34]. AIH patients who develop end-stage liver disease may require liver transplantation [40], and it is to note that five year patient and graft survivals are about 80–90%; recurrence of the disease may occur after transplantation. Post-transplant immune hepatitis or *de novo* AIH can occur after liver transplantation for diseases other than AIH [34].

3. Primary biliary cirrhosis

PBC is an autoimmune cholestatic liver disease characterized by progressive intra-hepatic bile duct destruction eventually leading to cirrhosis, liver failure, and eventually to liver transplantation or death [41] (Table 1). PBC is indeed a misnomer, since currently the main part of patients may not develop cirrhosis as the final event.

3.1. Geoepidemiology

Recent data coming from different geographical areas on surveys of diagnoses indicate that although PBC is still considered a rare disease its prevalence and incidence are apparently increasing (Table 3) [6]. It has been suggested that these observations are more likely the result of different methodologies for case finding in epidemiological studies and possibly the improved case finding strategies and easier recognition of the disease, rather than reflecting a true difference in the prevalence of PBC cases. More importantly, no solid population-based study has been performed thus far. Several recent epidemiological data in USA indicate an annual incidence rate of up to 30 cases per million population with prevalence rates of up to 400 cases per million population among the Caucasian population [42]; Lower prevalence and incidence have been reported in other countries, such as Canada, Australia, and the Mediterranean countries [43–51]. Interestingly, a population-based study performed in Australia showed that the prevalence rates of PBC were significantly higher for Italian, British, and Greek immigrants, compared to native population [52]. However, it remains to be determined whether ethnic differences are related to migratory fluxes or reflect solely the effects of genetics. While familial clustering strongly suggests a major role for genetic

Table 3

Selected studies of prevalence, incidence, and sex ratio in primary biliary cirrhosis.

Geographical area	Year	Number of cases	Incidence (per million)	Prevalence (per million)	Gender (M:F)	Reference
Europe	1984	569	4	23	1:10	[43]
Sweden	1985	111	13.3	151	1:6	[44]
Newcastle, UK	1989	347	19	154	1:9	[45]
Canada	1990	225	3.26	22	1:13	[46]
Victoria, Australia	1995	84	—	19	1:11	[47]
Estonia	1995	69	2.27	26.9	1:22	[48]
Norway	1998	21	16	146	1:9	[16]
USA	2000	46	27	402	1:8	[42]
Newcastle, UK	2001	770	31	251	1:10	[49]
Victoria, Australia	2004	249	—	51	1:10	[52]
Japan	2005	9761	—	78	1:9	[50]
Canada	2009	227	30	227	1:9	[51]

predisposition, no definitive data on the etiologic role of any specific environmental factors have come from epidemiology [53,54].

3.2. Etiopathogenesis

The serological hallmark of PBC is the presence of serum AMA, being present in up to 90% of patients with PBC [55]. However, a number of other autoantibodies, such as disease-specific ANA, can be present [31,32,56]. It is to note that several PBC-specific ANA disclosed a prognostic role [31,32,56]. Other than circulating autoantibodies, PBC is also characterized by the presence of autoreactive T and B cells to major antigens, such as the E2 subunit of the mitochondrial pyruvate dehydrogenase complex (PDC-E2) [6]. A role also for cells of the innate immunity system [6,57] and microRNA [58] is emerging. PBC is considered to result from a combination of environmental and genetic risk factors. Genetic predisposition is strongly suggested by the higher familial incidence of the disease and the high concordance rate among monozygotic twins [59,60]. In addition, a number of HLA (i.e. HLA-DRB1*08, -DRB1*11, DRB1*13) and non HLA loci have been found to be associated with the disease [18]. As many autoimmune disorders, also PBC is characterized by a striking female predominance (Table 3), with suggestions of a key role for X chromosome defects [61]. Indeed, it has been shown that women with PBC have a significantly enhanced frequency of monosomy X in circulating blood cells compared to age-matched healthy women [62] and that the X chromosome loss is preferential [63]. At the same time, many evidences support the role of environmental events in triggering the disruption of a pre-existing unstable immune tolerance. It is believed that initiating mimetopes of the PBC-specific epitope of the PDC-E2 can be derived from environmental xenobiotics able to modify the structure of native proteins or, alternatively, infectious agents that utilize this enzyme [64]. In the past 3 years, a number of spontaneous and two chemically-induced models of PBC were described which will surely help to clarify the disease pathogenesis in the near future [65].

3.3. Diagnosis

The diagnosis of PBC is based on (1) elevation of biochemical indices of cholestasis for more than six months, (2) the presence of serum AMA, and (3) typical histological pictures in the liver [2,41,54]. The presence of at least two of these criteria is needed for a probable diagnosis while the occurrence of all criteria allows a definite diagnosis. Of course, alternative diagnoses of liver disease have to be ruled out, particularly in AMA-negative patients; a nuclear magnetic resonance cholangiography is necessary to exclude a PSC.

In the past, the term “autoimmune cholangitis” has been proposed for a subset of PBC patients lacking AMA but positive for serum ANA and SMA. However, recent evidences suggest that these patients are affected by a disease not far different from classical PBC [32].

3.4. Histological features

The typical intra-hepatic lesion for PBC is a chronic non-suppurative destructive cholangitis involving small and medium interlobular bile ducts (max diameter 80 μ). The liver is not uniformly affected and is divided into four histological stages: Stage 1, characterized by inflammation to portal triads. Stage 2 with extension of inflammation beyond the portal triads into the lobular parenchyma and ductopenia. Stage 3 entails fibrous septa between adjacent portal tracts. Stage 4 characterized by liver cirrhosis.

3.5. Clinical features

In the last two decades, PBC is diagnosed more and more often at an earlier stage of disease and the large majority of patients are asymptomatic at the time of diagnosis [54]. Pruritus and fatigue are early symptoms of PBC which may occur in about 20% of the patients, and portal hypertension (i.e. ascites, variceal bleeding and hepatic encephalopathy) is its major complication. Although fatigue has been suggested as a specific symptom, a predominant psychogenic component, as generally occurs in carriers of chronic progressive diseases, is more likely. On the contrary, pruritus appears to be the most typical symptom of PBC, occurring in 20–70 percent of patients. Finally, although portal hypertension may occur even before the development of cirrhosis it usually complicates the course of PBC only in advanced stages. Other frequent findings in advanced PBC are the consequences of longstanding cholestasis that may lead to fat malabsorption, hyperlipidaemia, renal tubular acidosis and osteopenia.

3.6. Treatment

UDCA is the only accepted treatment for PBC [41,54]. UDCA comprises about 2% of human bile acids, acts as a choleric agent, and, at a dose of 12–15 mg per kilogram of body weight per day, can delay the progression of the disease [54]. Several other therapeutic agents have been tested for PBC and some interesting possibilities have been shown but mainly in combination treatment with UDCA. Regarding corticosteroids, data are scanty mainly because of bone demineralization in a population of female patients at post-menopausal age. Accordingly, monotherapy should be limited to patients with PBC-AIH overlap syndrome (see the dedicated paragraph in this chapter). Because of substantial risk of side-effects, azathioprine, cyclosporine and other immunosuppressive agents are not recommended. However, strategies aimed at improving treatments for PBC are still needed, mainly by mean of associated treatments. Recently, the results obtained with colchicine and budesonide are the more promising but none of the drug studied provided significant additional benefit, in terms of clinically relevant events, compared to UDCA monotherapy. Finally, liver transplantation is the only effective treatment in patients with very advanced disease being able to substantially improved survival. Indeed, the survival rates are 90% and 85% respectively at 1 and 5 years.

4. Primary sclerosing cholangitis

PSC is a rare cause of chronic liver disease characterized by chronic inflammation and obliterative fibrosis of the intra- and/or extra-hepatic biliary tree (Table 1), which leads to cholestasis, hepatic fibrosis and, ultimately, cirrhosis, end-stage liver disease and death [66–68]. Scanty data are available regarding the overall prevalence of PSC (Table 4). PSC is strongly associated (60–80%) with inflammatory bowel diseases (IBD), mainly ulcerative colitis

Table 4

Data on prevalence, incidence, and sex ratio in primary sclerosing cholangitis.

Geographical area	Year	Number of cases	Incidence (per million)	Prevalence (per million)	Gender (M:F)	Reference
Spain	1994	43	0.7	2.2	1:1	[71]
Norway	1998	17	13	85	2:1	[16]
Alaska, USA	2002	0	0	0	—	[72]
Singapore	2002	10	—	13	9:1	[73]
USA	2003	22	9	136	1.3:1	[70]
Wales, UK	2004	46	9	127	1.2:1	[74]

(80%) but also Crohn's disease (10%). Each patient with PSC should undergo a colonoscopy with biopsies since a diagnosis of IBD has relevant implications for follow-up. Indeed, patients with IBD and PSC have a higher risk of dysplasia and colon cancer compared to patients with IBD only. Its natural history is often complicated by the development of cholangiocarcinoma and other malignancies [69].

4.1. Geoepidemiology

Few data are available regarding the overall prevalence of PSC (Table 4). In the USA and Northern Europe, the estimated incidence of PSC is 0.9–1.3 cases per 100,000 population, while the prevalence in these areas ranges from 8 to 14 per 100,000 population [70–74].

4.2. Etiopathogenesis

The etiopathogenesis of PSC remains poorly understood, mainly because of its insidious onset which makes problematic the identification of aetiological factors [75]. PSC is considered to be immune mediated being associated with a number of serum autoantibodies and HLA haplotypes as well as being related to IBD and for the presence of lymphocytic infiltration into portal areas. In addition, evidence that PSC is immune mediated comes from the association of PSC with a number of autoimmune diseases. However, PSC cannot be considered a typical autoimmune disease, because of the male predominance and lacks of the characteristic response to immunosuppressive agents as seen in AIH.

4.3. Diagnosis

PSC is diagnosed in patients with elevated serum markers of cholestasis (i.e. alkaline phosphatase and gamma-glutamyl-traspeptidase) and the presence of typical bile duct changes, such as multifocal strictures and segmental dilatations at magnetic resonance cholangiopancreatography (MRCP) or endoscopic cholangiopancreatography (ERCP) [2,76]. Patients with normal cholangiogram but clinical, biochemical and histological features compatible with PSC are classified as small duct PSC. Criteria used to make diagnosis of PSC in adults also apply to children, although the presentation of PSC in children has frequently features similar to those of AIH [37].

4.4. Autoantibodies

A high proportion of non-specific autoantibodies, such as ANA, can be found in the sera of patients with PSC but are not helpful in diagnosis [77]. Among others, atypical pANCA are present in the serum of up to 90% patients with PSC, but are not specific being present also in patients with AIH, and ulcerative colitis. Atypical pANCA reacts to a myeloid specific nuclear protein with a molecular mass of 50 kDa by immunoblotting, thus the term pANNA (peripheral anti-neutrophil nuclear antibody) seems to be more appropriate. Unfortunately, the target antigen for pANNA is still unknown as the role of these autoantibodies in the etiopathogenesis of PSC. Finally, autoantibodies to surface antigens expressed on biliary epithelial cells are more frequently found in sera from patients with PSC than in patients with AIH, PBC, or normal controls.

4.5. Treatment

UDCA at a dose of 15–20 mg/day improves serum liver tests, but a proven benefit on survival is still lacking [2,76]. Accordingly, based on the available data it is not possible to suggest the general use of UDCA in PSC. Several studies suggest the use of UDCA for

chemoprevention of colorectal cancer in patients with PSC, particularly in patients with a strong family history of colorectal cancer, or longstanding colitis. Biliary dilatation or biliary stent insertion of dominant bile duct strictures with severe cholestasis are indicated. In patients with end-stage disease, cholangiocyte dysplasia or recurrent bacterial cholangitis, liver transplantation is highly recommended.

5. Overlap syndromes

Simultaneous or sequential occurrence of PBC and AIH, or PSC and AIH have been described in both adult and pediatric populations [2,4]. The reported prevalence of these overlap syndromes varies from 10 to 50% depending on the diagnostic scoring system used and the age of the study population.

5.1. PBC-AIH overlap syndrome

Diagnostic criteria for PBC-AIH overlap syndrome were proposed but are not generally accepted and used. A diagnosis of PBC-AIH overlap syndrome should always be considered in patients with PBC for the potential therapeutic implications. Patients with PBC-AIH overlap syndrome should be treated with a combined therapy with steroids and UDCA. For late stage disease, liver transplantation is the treatment of choice.

5.2. PSC-AIH overlap syndrome

PSC-AIH overlap syndrome is an immune-related disorder characterized by cholangiographic features of PSC and histological and serological findings typical of AIH. In general, PSC in children is characterized by more pronounced autoimmune features compared to adults, and it has been proposed “autoimmune sclerosing cholangitis in childhood” as more appropriate term [37]. UDCA and immunosuppressive therapy are the recommended treatment of AIH-PSC overlap syndrome, while liver transplantation is indicated for end-stage disease.

6. Immunoglobulin G4-associated cholangitis

Immunoglobulin G4-associated cholangitis (IAC) is a recently described corticosteroid-responsive biliary disease [2] (Table 1). The immunopathogenesis is unknown but an autoimmune nature is highly possible. Interestingly, IAC is a sclerosing cholangitis with a good long-term prognosis after response to immunosuppressive treatment (corticosteroids and/or azathioprine). IAC is never associated with IBD, frequently involves the extra-hepatic bile ducts, is often associated with autoimmune pancreatitis and other fibrosing conditions, and is characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells in bile ducts and liver tissue.

7. Concluding remarks

The field of ALD is clearly showing how the findings of basic science influence routine clinical practice in terms of diagnostic procedures, clinical management and prediction of outcome. However, as for other autoimmune disorders, also for ALD continuous effort should be performed. In particular, it will be important to collect additional information on the incidence and prevalence of these rare conditions in additional geographical regions, not only in the so-called developed countries. The completion of the sequencing of human genome together with the wide technical progresses have recently allowed the identification of new genetic risk variants in many autoimmune disorders. Again, after this current first wave of data from high-density genome-wide studies,

we now need to perform such studies also in patients with ALD in order to identify their major genetic factors. In addition, a role for sex chromosomes in the development of ALD needs to be confirmed and further characterized. Finally, in the future, the development of specific animal models for ALD will allow to clarify the underlying mechanisms of these diseases with the final goal to provide better tools for their clinical management and therapy.

References

- [1] Invernizzi P, Mackay IR. Autoimmune liver diseases. *World J Gastroenterol* 2008;14:3290–1.
- [2] EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol* 2009;51:237–67.
- [3] Manns MP, Vergani D. Autoimmune hepatitis. *Semin Liver Dis* 2009;29:239–40.
- [4] Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. *World J Gastroenterol* 2008;14:3368–73.
- [5] Davies AJ. Immunological tolerance and the autoimmune response. *Autoimmun Rev* 2008;7:538–43.
- [6] Lleo A, Battezzati PM, Selmi C, Gershwin ME, Podda M. Is autoimmunity a matter of sex? *Autoimmun Rev* 2008;7:626–30.
- [7] Boscolo P, Youinou P, Theoharides TC, Cerulli G, Conti P. Environmental and occupational stress and autoimmunity. *Autoimmun Rev* 2008;7:340–3.
- [8] Carambia A, Herkel J. CD4T cells in hepatic immune tolerance. *J Autoimmun* 2009 Aug 29. [Epub ahead of print].
- [9] Moritoki Y, Lian ZX, Ohsugi Y, Ueno Y, Gershwin ME. B cells and autoimmune liver diseases. *Autoimmun Rev* 2006;5:449–57.
- [10] Morahan G, Peeva V, Mehta M, Williams R. Systems genetics can provide new insights in to immune regulation and autoimmunity. *J Autoimmun* 2008;31:233–6.
- [11] Christen U, Hintermann E, Holdener M, von Herrath MG. Viral triggers for autoimmunity: is the 'glass of molecular mimicry' half full or half empty? *J Autoimmun* 2009 Aug 26 [Epub ahead of print].
- [12] Plebani M, Pittoni M, Celadin M, Bernardi D, Mion MM. Recent advances in diagnostic technologies for autoimmune diseases. *Autoimmun Rev* 2009;8:238–43.
- [13] Krawitt EL. Autoimmune hepatitis. *N Eng J Med* 2006;354:54–66.
- [14] Mackay IR. Historical reflections on autoimmune hepatitis. *World J Gastroenterol* 2008;14:3292–300.
- [15] Longhi MS, Ma Y, Mieli-Vergani G, Vergani D. Aetiopathogenesis of autoimmune hepatitis. *J Autoimmun* 2009 Sep 17. [Epub ahead of print].
- [16] Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998;33:99–103.
- [17] Primo J, Merino C, Fernandez J, Moles JR, Llorca P, Hinojosa J. [Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain)]. *Gastroenterologia Y Hepatologia* 2004;27:239–43.
- [18] Invernizzi P, Gershwin ME. The genetics of human autoimmune disease. *J Autoimmun* 2009;33:290–9.
- [19] McCluskey J, Peh CA. The human leucocyte antigens and clinical medicine: an overview. *Rev Immunogenet* 1999;1:3–20.
- [20] Donaldson PT. Genetics in autoimmune hepatitis. *Semin Liver Dis* 2002;22:353–64.
- [21] Carson DA. Genetic factors in the etiology and pathogenesis of autoimmunity. *FASEB J* 1992;6:2800–5.
- [22] Duarte-Rey C, Pardo AL, Rodriguez-Velosa Y, Mantilla RD, Anaya JM, Rojas-Villarraga A. HLA class II association with autoimmune hepatitis in Latin America: a meta-analysis. *Autoimmun Rev* 2009;8:325–31.
- [23] Vergani D, Mieli-Vergani G. Aetiopathogenesis of autoimmune hepatitis. *World J Gastroenterol* 2008;14:3306–12.
- [24] Ma Y, Okamoto M, Thomas MG, Bogdanos DP, Lopes AR, Portmann B, et al. Antibodies to conformational epitopes of soluble liver antigen define a severe form of autoimmune liver disease. *Hepatology* 2002;35:658–64.
- [25] Kerkar N, Choudhuri K, Ma Y, Mahmood A, Bogdanos DP, Muratori L, et al. Cytochrome P4502D6(193–212): a new immunodominant epitope and target of virus/self cross-reactivity in liver kidney microsomal autoantibody type 1-positive liver disease. *J Immunol* 2003;170:1481–9.
- [26] Longhi MS, Meda F, Wang P, Samyn M, Mieli-Vergani G, Vergani D, et al. Expansion and de novo generation of potentially therapeutic regulatory T cells in patients with autoimmune hepatitis. *Hepatology* 2008;47:581–91.
- [27] Christen U, Holdener M, Hintermann E. Animal models for autoimmune hepatitis. *Autoimmun Rev* 2007;6:306–11.
- [28] Holdener M, Hintermann E, Bayer M, Rhode A, Rodrigo E, Hintereder G, et al. Breaking tolerance to the natural human liver autoantigen cytochrome P450 2D6 by virus infection. *J Exp Med* 2008;205:1409–22.
- [29] Buxbaum J, Qian P, Allen PM, Peters MG. Hepatitis resulting from liver-specific expression and recognition of self-antigen. *J Autoimmun* 2008;31:208–15.
- [30] Czaja AJ, Bianchi FB, Carpenter HA, Krawitt EL, Lohse AW, Manns MP, et al. Treatment challenges and investigational opportunities in autoimmune hepatitis. *Hepatology* 2005;41:207–15.
- [31] Bogdanos DP, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. *World J Gastroenterol* 2008;14:3374–87.
- [32] Invernizzi P, Lleo A, Podda M. Interpreting serological tests in diagnosing autoimmune liver diseases. *Semin Liver Dis* 2007;27:161–72.
- [33] Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48:169–76.
- [34] Krawitt EL. Clinical features and management of autoimmune hepatitis. *World J Gastroenterol* 2008;14:3301–5.
- [35] Bridoux-Henno L, Maggiore G, Johanet C, Fabre M, Vajro P, Dommergues JP, et al. Features and outcome of autoimmune hepatitis type 2 presenting with isolated positivity for anti-liver cytosol antibody. *Clin Gastroenterol Hepatol* 2004;2:825–30.
- [36] Al-Chalabi T, Boccato S, Portmann BC, McFarlane IG, Heneghan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. *J Hepatol* 2006;45:575–83.
- [37] Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol* 2008;14:3360–7.
- [38] Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thio-purine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. *J Hepatol* 2006;45:584–91.
- [39] Montano-Loza AJ, Carpenter HA, Czaja AJ. Improving the end point of corticosteroid therapy in type 1 autoimmune hepatitis to reduce the frequency of relapse. *Am J Gastroenterol* 2007;102:1005–12.
- [40] Mottershead M, Neuberger J. Transplantation in autoimmune liver diseases. *World J Gastroenterol* 2008;14:3388–95.
- [41] Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Eng J Med* 2005;353:1261–73.
- [42] Kim WR, Lindor KD, Locke 3rd GR, Thorneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology* 2000;119:1631–6.
- [43] Triger DR, Berg PA, Rodes J. Epidemiology of primary biliary cirrhosis. *Liver* 1984;4:195–200.
- [44] Lofgren J, Jarnerot G, Danielsson D, Hemdal I. Incidence and prevalence of primary biliary cirrhosis in a defined population in Sweden. *Scand J Gastroenterol* 1985;20:647–50.
- [45] Mysor M, James OF. The epidemiology of primary biliary cirrhosis in north-east England: an increasingly common disease? *Q J Med* 1990;75:377–85.
- [46] Witt-Sullivan H, Heathcote J, Cauch K, Blendis L, Ghent C, Katz A, et al. The demography of primary biliary cirrhosis in Ontario, Canada. *Hepatology* 1990;12:98–105.
- [47] Watson RG, Angus PW, Dewar M, Goss B, Sewell RB, Smallwood RA. Low prevalence of primary biliary cirrhosis in Victoria, Australia. *Melbourne Liver Group. Gut* 1995;36:927–30.
- [48] Rimmel T, Rimmel H, Uibo R, Salupere V. Primary biliary cirrhosis in Estonia. With special reference to incidence, prevalence, clinical features, and outcome. *Scand J Gastroenterol* 1995;30:367–71.
- [49] Prince MI, Chetwynd A, Diggle P, Jarner M, Metcalf JV, James OF. The geographical distribution of primary biliary cirrhosis in a well-defined cohort. *Hepatology* 2001;34:1083–8.
- [50] Sakauchi F, Mori M, Zeniya M, Toda G. A cross-sectional study of primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. *J Epidemiol* 2005;15:24–8.
- [51] Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. *Hepatology* 2009.
- [52] Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. *Gastroenterology* 2004;127:470–5.
- [53] Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatology* 2005;42:1194–202.
- [54] Crosignani A, Battezzati PM, Invernizzi P, Selmi C, Prina E, Podda M. Clinical features and management of primary biliary cirrhosis. *World J Gastroenterol* 2008;14:3313–27.
- [55] Gershwin ME, Mackay IR. The causes of primary biliary cirrhosis: convenient and inconvenient truths. *Hepatology* 2008;47:737–45.
- [56] Invernizzi P, Selmi C, Ranftler C, Podda M, Wesiarska-Gadek J. Antinuclear antibodies in primary biliary cirrhosis. *Semin Liver Dis* 2005;25:298–310.
- [57] Lan RY, Salunga TL, Tsuneyama K, Lian ZX, Yang GX, Hsu W, et al. Hepatic IL-17 responses in human and murine primary biliary cirrhosis. *J Autoimmun* 2009;32:43–51.
- [58] Padgett KA, Lan RY, Leung PC, Lleo A, Dawson K, Pfeiff J, et al. Primary biliary cirrhosis is associated with altered hepatic microRNA expression. *J Autoimmun* 2009;32:246–53.
- [59] Selmi C, Invernizzi P, Zuin M, Podda M, Gershwin ME. Genetics and geo-epidemiology of primary biliary cirrhosis: following the footprints to disease etiology. *Semin Liver Dis* 2005;25:265–80.
- [60] Invernizzi P, Selmi C, Mackay IR, Podda M, Gershwin ME. From bases to basis: linking genetics to causation in primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2005;3:401–10.

- [61] Invernizzi P, Pasini S, Selmi C, Gershwin ME, Podda M. Female predominance and X chromosome defects in autoimmune diseases. *J Autoimmun* 2009; 33:12–6.
- [62] Invernizzi P, Miozzo M, Battezzati PM, Bianchi I, Grati FR, Simoni G, et al. Frequency of monosomy X in women with primary biliary cirrhosis. *Lancet* 2004;363:533–5.
- [63] Miozzo M, Selmi C, Gentilin B, Grati FR, Sirchia S, Oertelt S, et al. Preferential X chromosome loss but random inactivation characterize primary biliary cirrhosis. *Hepatology* 2007;46:456–62.
- [64] Selmi C, Gershwin ME. The role of environmental factors in primary biliary cirrhosis. *Trends Immunol* 2009;30:415–20.
- [65] Chuang YH, Ridgway WM, Ueno Y, Gershwin ME. Animal models of primary biliary cirrhosis. *Clin Liver Dis* 2008;12:333–47.
- [66] Lee YM, Kaplan MM. Primary sclerosing cholangitis. *N Eng J Med* 1995;332:924–33.
- [67] Cullen SN, Chapman RW. The medical management of primary sclerosing cholangitis. *Semin Liver Dis* 2006;26:52–61.
- [68] Maggs JR, Chapman RW. An update on primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2008;24:377–83.
- [69] Lazaridis KN, Gores GJ. Primary sclerosing cholangitis and cholangiocarcinoma. *Semin Liver Dis* 2006;26:42–51.
- [70] Bambha K, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology* 2003;125:1364–9.
- [71] Escorsell A, Pares A, Rodes J, Solis-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. Spanish Association for the Study of the Liver. *J Hepatol* 1994;21:787–91.
- [72] Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. *Am J Gastroenterol* 2002;97:2402–7.
- [73] Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan JY. Clinical profile of primary sclerosing cholangitis in Singapore. *J Gastroenterol Hepatol* 2002;17:908–13.
- [74] Kingham JG, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. *Gastroenterology* 2004;126:1929–30.
- [75] Chapman R, Cullen S. Etiopathogenesis of primary sclerosing cholangitis. *World J Gastroenterol* 2008;14:3350–9.
- [76] Silveira MG, Lindor KD. Clinical features and management of primary sclerosing cholangitis. *World J Gastroenterol* 2008;14:3338–49.
- [77] Hov JR, Boberg KM, Karlsen TH. Autoantibodies in primary sclerosing cholangitis. *World J Gastroenterol* 2008;14:3781–91.