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Review

Clinical management of autoimmune biliary diseases

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ABSTRACT

Autoimmune biliary disease is an umbrella term that encompasses several distinct entities such as primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis and overlap syndromes. The general approach to the diagnosis of these disorders involves investigating symptomatic patients presenting with a cholestatic biochemical profile. Asymptomatic patients are often diagnosed during investigation of other accompanying or discrete diseases. The distinction between the various entities is necessary for directing clinical management in this group of patients with an underlying autoimmune pathophysiology. Goals of management comprise treating symptoms, preventing complications and suppressing the underlying pathogenetic processes. Liver transplantation plays a vital role in the management of this group of patients and has shown a dramatic improvement in outcomes. Medical therapies such as ursodeoxycholic acid have shown mixed effects with excellent outcomes in primary biliary cirrhosis and less impressive results in primary sclerosing cholangitis. In this manuscript we aim to discuss in detail the management of these autoimmune biliary disorders and describe the effects of different therapies on outcomes on the different subsets of patients.

1. Introduction

The clinical management of autoimmune biliary diseases can be challenging. This is, in part, due to the complex pathogenesis involved with these disease entities, the lack of effective medical therapy in some cases, and the wide array of associated complications affecting susceptible individuals. For patients with conditions where effective medical therapy exists, there can be dilemmas in management based on incomplete or ineffective treatment responses and continued progression of the disease despite timely intervention. As novel studies help clarify the pathogenesis underlying these multifaceted disorders, the emergence of new paradigms for medical management is predicted.

In this review, we will provide an update on the clinical epidemiology and management of autoimmune biliary disorders. In addition, we will suggest a general approach for diagnosing these autoimmune diseases and address current pitfalls in clinical management.

2. Epidemiology and pathogenesis of autoimmune biliary diseases

2.1. Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic liver disease predominantly diagnosed in females between their 5th and 6th decades of life [1]. The estimated incidence of PBC in the US is amongst the highest compared to other countries with an estimated incidence of 4.5 (95% confidence interval: 3.1–5.9) for women, 0.7 (95% CI, 0.1–1.3) for men, and 2.7 (95% confidence interval: 1.9–3.5) overall [2]. Histologically, PBC is characterized by the pathological destruction of small and medium bile ducts culminating in end stage liver disease and the need for liver transplantation in some individuals [2].

The proposed pathogenesis of PBC has been greatly debated, with several data sources available supporting an autoimmune component related to disease pathology. The different proposed mechanisms are shown in Table 1.

2.2. Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology that is often diagnosed in the fifth

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Table 1
The various proposed mechanisms of PBC pathogenesis.

Proposed mechanisms of pathogenesis	Evidence
Autoimmune	1) Circulating antibodies in the serum of PBC patients. 2) Elevated serum immunoglobulin levels. 3) Strong associations with extrahepatic autoimmune diseases. 4) Development of granulomas in the liver and lymph nodes [3].
Environmental	1) Exposure to tobacco smoke may lead to the development of PBC. 2) Urinary tract infections and chemical xenobiotics also occur in high frequencies among subjects developing PBC as compared to controls [4,5].
Genetic	1) Susceptibility loci for PBC [6]. 2) Fc receptor-like 3 (FCRL3) gene shows predominance in persons of Asian ethnicity [7]. 3) Tumor necrosis factor (TNF) signaling and B cell differentiation [8].

decade of life among patients with concurrent inflammatory bowel disease (IBD) [9]. The disease affects males and females at a ratio of 2:1 [10]. Hallmark features of PSC include progressive intrahepatic and extrahepatic bile duct stricturing leading to cirrhosis and end stage liver disease [10].

Current understanding of the clinical epidemiology of PSC is well illustrated by an interesting study performed in Southern Sweden which showed a three fold increase in the incidence of PSC between 1992 and 2005 [11]. This study also reported an incidence was 1.22/100,000 person years overall. The incidence in males and females was 1.78 and 0.69 per 100,000 person years respectively. Overall the point prevalence of PSC by the end of 2005 was 16.2 per 100,000. 23.7 and 8.9 per 100,000 men and women respectively had PSC at the end of 2005 in that patient population. In Olmsted County, Minnesota, the prevalence of PSC in the year 2000 was estimated at 20.9 cases and 6.3 cases per 100,000 men and women respectively. Furthermore, age adjusted incidence of PSC was estimated at 1.25 (95% CI, 0.70–2.06) and 0.54 (95% CI, 0.22–1.12) per 100,000 person years for men and women respectively and the 0.90 per 100,000 person years (95% CI, 0.56–1.36) overall. The estimated prevalence of IBD was 73% with 75% of patients having ulcerative colitis [12]. Another study by Kaplan et al. identified an age and gender adjusted annual incidence rate of 0.92 cases per 100,000 person years amongst all residents of Calgary health region in Alberta Canada between 2000 and 2005 [13]. Notably, a recent meta-analysis concluded that the incidence of PSC is estimated at 0.77 per 100,000 person years and shows an increasing occurrence of PSC over time [14].

The pathogenesis of PSC is suspected to involve several mechanisms with immune-mediated processes, bacterial infection, and genetic susceptibility being the major categories of interest. A number of observations suggest an immune-mediated pathogenesis for PSC including an increased frequency of serum autoantibodies including anti-nuclear antibodies (ANA), anti-smooth muscle autoantibodies (ASMA) and antineutrophil cytoplasmic antibodies (p-ANCA). Furthermore, PSC is strongly associated with multiple extrahepatic autoimmune diseases including celiac disease, rheumatoid arthritis, Sjögren's syndrome and thyroiditis [15–18].

In terms of genetic predisposition, human leukocyte antigen (HLA) loci are greatly associated with PSC. HLA B8 and DR3 show strong association with PSC in more than 50% of cases, whereas, HLA Dr3w52a is associated with PSC in up to 100% of patients diagnosed with PSC. Conversely, Dr2 is seen in younger patients. HLA subtypes have also been associated with prognosis where DR4 predicts worse outcomes in patients with PSC [19–22].

Genome wide association studies in PSC have shown several susceptibility loci. A novel study looking at genome wide associations in sclerosing cholangitis and UC identified that **G protein-coupled receptor 35 (**GPR35) conveys a risk for both PSC and UC and **Transcription factor 4** (TCF4) is associated with risk for PSC but not UC [23]. Recently, a study from Cambridge assessing risk loci for PSC present in 992 patients as compared to 5162 controls concluded that a role may exist for **interleukin 2 (IL2) receptor alpha (IL2RA)** IL-2/IL2RA pathway in PSC and also confirmed association of macrophage stimulating 1 (MST1) [24]. Current GWAS studies are constantly identifying new loci that preclude a risk for PSC and in the near future a better understanding of genetic predisposition of PSC and other cholestatic diseases will be possible [25].

Overproduction of tumor necrosis factor due to Kupffer cell activation by bacterial toxins which leads to portal fibrosis presents the cornerstone for the hypothesis of bacterial involvement in the pathogenesis of PSC [26]. This theory however is contradicted by the fact that development of PSC is independent of ulcerative colitis which is thought to be the major contributor to bacterial toxin production in PSC patients [27]. Similarly, an older theory on viral involvement in the pathogenesis of PSC remains weak and needs further investigation [28].

2.3. Autoimmune hepatitis

Autoimmune hepatitis (AIH) was first described in 1950 by Waldenström in young women presenting with infiltration of the liver with plasma cells, cirrhosis and elevated levels of immunoglobulin G (IgG) [29]. Reports through the 1950's helped further define features of AIH which include acne, hirsutism, amenorrhea, jaundice, hepatosplenomegaly, and the presence of disease-specific circulating autoantibodies [30].

Despite manifesting as a chronic hepatitis in most patients, AIH can sometimes develop acutely. An important feature of AIH is its responsiveness to corticosteroid therapy, reflected by the excellent outcomes achieved upon institution of proper management as compared to cirrhosis and fulminant hepatic failure with no treatment. Despite being first described in females, autoimmune hepatitis can affect both sexes and all ages. Triggers for the development of autoimmune hepatitis may include medications and infections. In 1993 the International Autoimmune Group produced a report in which criteria for diagnosis of autoimmune hepatitis were established [31].

Like many chronic liver diseases autoimmune hepatitis has both genetic predisposition and environmental triggers. Specific human leukocyte antigen haplotypes (HLA) were found to be associated with the development of AIH. Gene deletions were also described as related to disease progression in younger patients [32]. HLA haplotypes can also predict prognosis where patients with HLA DR3 or HLA DR4 may suffer a more aggressive disease course or increased extrahepatic manifestations respectively [33]. A recent study eludes to the involvement of non-classic major histocompatibility complex genes including genetic polymorphisms of CTLA-4, TNF-alpha, TBX21, TGF-beta1, Fas and VDR [34]. Moreover, antibodies to ribonucleoprotein 52 have been shown to reflect poor prognosis in patients with autoimmune hepatitis [35]. Anti-p53 has recently emerged as a helpful factor to differentiate AIH or AIH/PBC overlap from classic PBC [36].

3. General approach to diagnosis of autoimmune biliary diseases

Autoimmune liver disease often shows a cholestatic biochemical profile and is characterized by chronicity (>6 months). Cholestasis is a term used to coin disease processes affecting the formation or