Primary sclerosing cholangitis and primary biliary cirrhosis: epidemiology, risk factors, and outcome

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Introduction

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Large population-based studies on incidence and prevalence, as well as on the natural history of the major chronic cholestatic liver diseases - primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) - are scarce, but very important for appropriate patient counselling and finding clues to etiology of the diseases. In 2006 we initiated a multicenter study in 44 hospitals in the Netherlands to obtain precise population-based prevalence and incidence figures; insight into disease course with regard to survival; the need for liver transplantation; and occurrence of malignancies, as well as risk factors thereof.

PRIMARY SCLEROSING CHOLANGITIS

PSC is a cholestatic liver disease of unknown etiology. Chronic inflammation of the intra- and extrahepatic bile ducts leads to bile duct destruction, cholestasis, liver fibrosis and progression to end-stage liver disease. From the moment patients are diagnosed with PSC, years of treatment with endoscopic dilatation, imaging, blood tests and annual colonoscopies will follow; and many patients ultimately need a liver transplant.

Epidemiology

PSC is more common in men than in women (2:1) and can manifest itself at any age, with a peak incidence around the age of 40. Up to 80% of PSC patients - depending on geographic location - have concomitant inflammatory bowel disease (IBD) with a distinct phenotype. Several studies have investigated the epidemiology of PSC using different case-finding and case-ascertainment strategies. The reported incidence and prevalence figures show notable variation, depending on the applied search strategy, the population under study, and the scrutiny of case-finding and ascertainment. The literature on incidence and prevalence rates around the globe is systematically reviewed in chapter 2 followed by an evaluation of the largest population-based PSC cohort to date in chapter 3.

Diagnosis

Roughly 50% of PSC patients present with symptoms such as pruritus, fatigue, pain in the right upper abdomen, or episodes of fever and cold chills. On physical examination, hepatomegaly and splenomegaly are the main findings, but these are found in a minority of patients. Blood analysis shows elevated alkaline phosphatase (AP) and γ-glutamyl transferase (γ-GT) levels, and an increased IgG concentration in more than half the patients. In 70% of patients serum bilirubin concentrations are not elevated at the time of diagnosis. Atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA), anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies are linked to PSC, but are not disease-specific. The larger bile ducts, both intrahepatic and extrahepatic, are visualised using imaging techniques such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). Until recently, ERCP was primarily used to diagnose PSC. A major disadvantage of ERCP is the risk of post-ERCP pancreatitis and/or cholangitis. Nowadays, the quality of non-invasive MRCP is usually sufficient to visualise the bile ducts without the disadvantages of an invasive procedure. Multifocal strictures and saccular dilatations of the intra- and/or extrahepatic bile ducts seen on cholangiography are hallmarks of PSC (fig. 1.1), although this so-called ‘beading’ can also be found in secondary sclerosing cholangitis due to choledolithiasis, biliary surgery, IgG4-associated cholangitis, and various other causes. Liver biopsy is of limited value. Often non-specific changes of the small bile ductules are found, and there is a high probability of sampling error. A liver biopsy may help if there is evidence of small-duct PSC or an overlap syndrome with autoimmune hepatitis. Small-duct PSC is characterised by cholestatic and histopathological features of PSC, but normal bile ducts on cholangiography. Other causes of bile duct strictures such as cholangiocarcinoma, recurrent bile duct stones or IgG4-associated cholangitis should be excluded before diagnosing PSC. The AASLD practice guideline on the diagnosis and management of PSC suggested measuring serum IgG4 in all patients with possible PSC, to exclude IAC.

Chapter 6 addresses the diagnostic dilemma of elevated serum IgG4 in differentiating patients with a chronic cholangiopathy otherwise compatible with PSC or IAC.
Pathogenesis
PSC is considered to be a complex genetic disease meaning that environmental factors trigger disease in a genetically predisposed individual. Several haplotypes of the HLA system have been associated with PSC, IBD and autoimmunity in general. Currently, 16 risk loci outside the HLA system have been identified in PSC. Some of these risk loci are associated with IBD, yet not all, suggesting a distinct genetic architecture. The strong association with IBD and the presence of gut-specific lymphocytes, chemokines, integrins, and addressins in liver biopsies and explanted livers of PSC patients has led to the hypothesis that PSC is an extra-intestinal manifestation of IBD. Colitis in PSC patients is reported to behave differently than other types of IBD in that it often runs a mild course, and the inflammation is predominantly located in the right colon. Chapter 4 reports how the phenotype of IBD in PSC patients was assessed using endoscopic and histopathologic criteria. IBD is considered to be the most important risk factor for PSC, yet little is known about environmental factors triggering the disease. In chapter 5, risk factors for developing PSC are assessed.

Disease course
Liver transplantation is the only available cure for PSC, although PSC can recur in the transplanted liver. Unfortunately, patients often die on the waiting list for liver transplantation, or they do not meet the criteria for receiving a donor liver. PSC patients are not only threatened by imminent liver failure, but also run an increased risk of developing colorectal cancer and cholangiocarcinoma. Survival, risk of malignancies and risk factors thereof, as well as the effectiveness of surveillance are described in chapter 3.

PRIMARY BILIARY CIRRHOSIS
PBC is a chronic cholestatic liver disease of the small and medium-sized intrahepatic bile ducts, affecting predominantly middle-aged or elderly women. PBC is considered to be an autoimmune disease due to the presence of antimitochondrial antibodies (AMA) directed against the E2 subunit of the pyruvate dehydrogenase complex, an enzyme complex found in mitochondria.

Epidemiology
PBC is more common in women than in men (male:female 1:9) with a peak incidence around the age of 60. Prevalence rates vary widely depending on location and search strategy. The incidence and prevalence rates around the world are reviewed in chapter 2. In chapter 7 we describe the population-based epidemiology of PBC in a large geographically defined area of the Netherlands.

Diagnosis
Similarly to PSC, about 50% of patients present with symptoms such as pruritus, fatigue or jaundice. The diagnosis of PBC is based on elevation of alkaline phosphatase (AP) of liver origin, and the presence of AMA in serum. Histological features of florid bile duct lesions support the diagnosis.

Pathogenesis
PBC is an autoimmune disease most likely triggered by environmental factors in genetically susceptible individuals. The striking female predominance in PBC and autoimmune diseases in general has led to the hypothesis that female-related factors may trigger disease. Intrinsic, environmental, and behavioural risk factors for PBC are assessed in chapter 7.

Disease course and treatment
In general, PBC patients respond very well to treatment with ursodeoxycholic acid (UDCA), a hydrophilic bile acid that has been shown to improve biochemical and histological markers, and subsequently to slow progression and improve survival. When medical therapy was not yet available for PBC, the estimated median survival from diagnosis until death was 8.4 years. Nowadays, the overall mortality is comparable to that in the general population, yet patients are at slightly increased risk of developing cancer, as discussed in chapter 8.

The unique setting in the Netherlands, with many people living in close proximity to high-quality care and excellent collaboration of gastroenterologists and hepatologists, allowed for inclusion of two large cohorts of PSC and PBC patients. This multicenter project enabled us to precisely study the epidemiology and disease course of PSC and PBC. The results of those studies are described in this thesis.
REFERENCES


