Inflammatory Bowel Disease Is Associated With Poor Outcomes of Patients With Primary Sclerosing Cholangitis

JING HIENG NGU,*,‡ RICHARD BLAIR GEARRY,*,‡ ANDREW JEFFREY WRIGHT,‡ and CATHERINE ANN MALCOLM STEDMAN*,‡

*Department of Gastroenterology, Christchurch Hospital, Christchurch; and ‡University of Otago, Christchurch, Canterbury, New Zealand

This article has an accompanying continuing medical education activity on page e135. Learning Objectives—At the end of this activity, the learner will recognize differences in the characteristics and outcomes of primary sclerosing cholangitis in patients with and without inflammatory bowel disease.

BACKGROUND & AIMS: Little is known about the exact etiology of primary sclerosing cholangitis (PSC); epidemiologic data are scarce. We performed a population-based epidemiologic study of PSC in Canterbury, New Zealand. **METHODS:** By using multiple case-finding methods, we searched public and private adult and pediatric outpatient clinics, hospital discharge summaries, and radiology and pathology reports to identify all cases of PSC in the region. Cases were included if PSC was identified by endoscopic retrograde cholangiography, magnetic resonance cholangiography, or liver biopsy analysis (n = 79). **RESULTS:** The incidence of PSC in 2008 was 1.6 per 100,000 persons (95% confidence interval [CI], 0.5–2.7). The point prevalence on December 31, 2008, was 11.7 per 100,000 persons (95% CI, 8.7–14.8). The mean and median ages at diagnosis were 50 years (95% CI, 46–53 years) and 49 years (range, 17–80 years), respectively. Patients who had inflammatory bowel disease (IBD) presented with PSC earlier than those without IBD ($P = .003$), were more likely to develop serious malignant complications ($P = .017$), and were more likely to require liver transplantation or die ($P = .03$). **CONCLUSIONS: In a population-based epidemiology study of PSC in Canterbury, New Zealand, we observed large differences between PSC patients with or without concurrent IBD in age at diagnosis, development of cancer, mortality, and requirement for liver transplantation. IBD therefore affects outcomes of patients with PSC, an important observation that requires further study.**

Keywords: Inflammation; Cancer Risk; Mortality; Autoimmune Liver Disease; Biliary Duct; Fibrosis.

Watch this article's video abstract and others at http://tiny.cc/bz9jv.

Scan the quick response (QR) code to the left with your mobile device to watch this article's video abstract and others. Don't have a QR code reader? Get one at mobiletag.com/en/download.php.

Primary sclerosing cholangitis (PSC) is a chronic progressive cholestatic liver disease of presumed autoimmune etiology, but its exact pathogenesis remains unknown. It is characterized by inflammation and fibrosis of the biliary ducts that lead to progressive cholestasis and cirrhosis of the liver as well as an increased risk of hepatobiliary and colorectal malignancies.[1–5] Hence, PSC is associated with significant morbidity and mortality with decreased survival despite the rescue option of liver transplantation.[6–9]

Population-based epidemiologic data concerning PSC are scarce. Epidemiologic studies can offer important insights into disease pathogenesis and provide an estimation of disease burden. To date, only a handful of population-based studies have investigated the epidemiology of PSC. These studies, which were performed in Norway,[10] United States,[11] United Kingdom,[6,12] Sweden,[13] and Canada,[14] report PSC incidences of 0.9–1.3/100,000 and prevalences of 8.5–16.2/100,000. However, population-based epidemiology of PSC has not been systematically examined in the Southern Hemisphere or the Asia Pacific region.

It is well-established that PSC is strongly associated with inflammatory bowel disease (IBD).[15,16] The prevalence of IBD in PSC is reported to be between 20% and 80%,[6,10–14,17–22] with a higher prevalence in white-predominant populations compared with Asian populations.[23] Previous reports have shown differences between the characteristics of PSC associated with IBD and PSC occurring in the absence of IBD. For example, the male-to-female ratio has been shown to be lower in patients without IBD, and combined intrahepatic and extrahepatic bile duct involvement was found more frequently in patients with IBD.[15,24] However, the exact relationship between IBD and PSC with regard to pathogenesis, clinical phenotype, and prognosis remains unclear. In addition, these relationships have yet to be examined in a population-based cohort.

Canterbury lies on the east coast of the South Island of New Zealand. It is New Zealand's largest province by area and second largest by population. Exhaustive epidemiology studies of other autoimmune diseases that have been performed in Canterbury such as autoimmune hepatitis,[25] IBD,[26] multiple sclerosis,[27] and

Abbreviations used in this paper: CI, confidence interval; ERC, endoscopic retrograde cholangiography; IBD, inflammatory bowel disease; MRC, magnetic resonance cholangiography; MST1, macrophage-stimulating 1; PSC, primary sclerosing cholangitis; WHO, World Health Organization.

1542-3565/$36.00
doi:10.1016/j.cgh.2011.08.027

Wegener granulomatosis[28] have found a high incidence and prevalence of these autoimmune diseases. Therefore, we aimed to conduct a population-based descriptive epidemiologic study of PSC in Canterbury, New Zealand. Our secondary aim was to compare the epidemiology, phenotype, and prognosis of PSC in patient cohorts with and without concurrent IBD.

Patients and Methods

Study Population

This study was conducted in the geographically defined region of Canterbury, New Zealand. It is located between latitude 42°S and 45°S and corresponds with 7 Territorial Local Authorities. It has defined boundaries that correlate with the National Census boundaries and is relatively geographically isolated. Therefore, reliable demographic information of the study population can be obtained from the Department of Statistics New Zealand based on data from the National Census. The estimated population for this region in 2008 was 494,170, which comprised 12% of the total New Zealand population. Approximately 75% of the Canterbury population lives within the Christchurch urban boundary. The majority of the population are of European descent (83%), after settlement predominantly from the United Kingdom and Ireland beginning in the 1840s. The remainder of the population comprises Maori (8%), Asian (6%), Pacific Islanders (2%) and other (1%).

Case Identification

Christchurch Hospital is a tertiary teaching hospital and is the only public hospital in this region that provides gastroenterology and hepatology services. There are 9 adult gastroenterologists and 1 pediatric gastroenterologist providing services to this region, and all private gastroenterologists in Canterbury also work at Christchurch Hospital. The public health system is used by the majority of New Zealand residents, although 32% of the population are covered by private health insurance.[29] Therefore, to ensure that all diagnosed PSC cases in the region were included in the study, patients from both public and private clinics and hospitals would need to be identified.

Cases were recruited both prospectively and retrospectively. Multiple case-finding strategies were used to identify retrospectively all known cases of PSC in Canterbury diagnosed between January 1, 1980 and December 31, 2006. All 9 adult and 1 pediatric gastroenterologists who provide services to this region were requested to identify all PSC patients under their care. All public and private adult and pediatric outpatient letters and hospital discharge summaries in Canterbury were searched to identify any patients with a clinical diagnosis of PSC. Radiology and pathology databases were also searched to identify any reports with a diagnosis of PSC on endoscopic retrograde cholangiography (ERC), magnetic resonance cholangiography (MRC), or liver biopsy.

From 2007–2008, cases were recruited prospectively. Whenever a new diagnosis of PSC was made in Canterbury during the study period, the investigators were informed, and cases were included in the study.

Case Ascertainment

Demographic and clinical data and laboratory, radiology, and histology results were extracted from paper and computer case notes. Cases were defined by using the Mayo criteria.[11,13] Large-duct PSC was defined as (1) clinical cholestasis with persistently elevated serum alkaline phosphatase levels for more than 6 months, (2) characteristic radiographic appearance of sclerosing cholangitis on ERC or MRC, and (3) no evidence of secondary sclerosing cholangitis. Small-duct PSC was defined when there were histologic features consistent with PSC on liver biopsy in the absence of characteristic radiologic features, and Mayo criteria 1 and 3 were present. Cases were included in the study if these criteria were fulfilled. The date of diagnosis was taken as that on which a definitive procedure (eg, ERC, MRC, or liver biopsy) that led to the diagnosis of PSC was performed. The diagnosis of IBD was confirmed according to recognized and accepted criteria.[30]

Statistical Analysis

The prospective PSC incidence rate was calculated for the period January 1, 2008–December 31, 2008. Prevalence was described as point prevalence on December 31, 2008. Retrospective incidence rates were calculated from 2001–2007. Incidence and prevalence were age-standardized to the World Health Organization (WHO) world standard population to allow for international comparison. Confidence intervals (CIs) were calculated. Comparisons between groups were made by using χ^2 test; when expected frequencies were small (<5), Fisher exact test was used.

Ethics

This study received ethical approval from the Upper South B Regional Ethics Committee.

Results

Characteristics of Primary Sclerosing Cholangitis Patients in Canterbury

A total of 79 patients with PSC were identified in Canterbury until December 31, 2008. Seventy-six cases (96%) were defined as large-duct PSC, and 3 cases were defined as small-duct PSC. The majority of large-duct PSC cases were diagnosed by ERC (62%), and 36% were diagnosed by MRC. Cases of small-duct PSC were diagnosed by liver biopsy. There was a male predominance, with 49 male (62%) and 30 female (38%) PSC patients identified. Nearly all patients (99%) were white, except for 1 patient who was of Maori descent. Five patients (6%) had overlap syndrome with autoimmune hepatitis. A total of 60 patients (76%) had concurrent IBD. Of these, 38 patients had ulcerative colitis (63%), 20 patients had Crohn's disease (33%), and 1 patient had indeterminate colitis. Patients were followed for a total of 613 person-years. There were a total of 22 deaths, and 7 patients underwent liver transplantation.

High Incidence and Prevalence of Primary Sclerosing Cholangitis in Canterbury

The prospective crude incidence rate was determined for 2008. Between January 1, 2008 and December 31, 2008, 8 new cases of PSC were diagnosed in the Canterbury region. Therefore, the prospective crude incidence rate of PSC in Canterbury in 2008 was 1.6 (95% CI, 0.5–2.7) per 100,000. Gender-adjusted incidence rates were 2.0 (95% CI, 0.6–4.6) per 100,000 for male and 0.8 (95% CI, 0.1–2.9) per 100,000 for female. Annual incidence rates were calculated from 2001–2008, with a