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Review

Geoepidemiology of primary sclerosing cholangitis: A critical review

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ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin, characterized by progressive destruction of bile ducts caused by diffuse inflammation and fibrosis. Previous epidemiological studies in Northern Europe and North America demonstrated that incidence and prevalence rates are ranging from 0.5 to 1.3 and from 3.85 to 16.2 per 100,000 inhabitants per year, respectively. It is of note that the incidence of PSC appears to be gradually increasing. We have extensively reviewed the geoepidemiology of PSC and attempted to place it in context with the incidence in Japan. In 2012, the clinical diagnostic criteria of IgG4-SC were established and published by the Japan Biliary Association, rendering it possible for physicians to clinically differentiate PSC from IgG4-SC. We conducted a new nationwide survey for PSC as well as IgG4-SC, and have identified 197 patients with PSC and 43 patients with IgG4-SC without pancreatic involvement. In this survey we estimated prevalence rate of PSC in Japan as 0.95, lower than those in North America and European countries. Also we identified other unique features of Japanese PSC patients, including 2 peaks in age distribution at diagnosis and fewer presences of comorbid inflammatory bowel diseases, occurring in only 34% of PSC. This data is placed in the perspective of the international experience on PSC.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin, characterized by the progressive destruction of bile ducts caused by diffuse inflammation and fibrosis that eventually leads to liver cirrhosis [1]. The etiopathogenesis of PSC has not been fully understood, and therefore epidemiological studies of PSC are of vital importance to reduce a significant burden to the health care system posed by PSC [2,3]. So far several epidemiological studies have been performed mainly in Northern Europe and North America to elucidate the incidence and prevalence of PSC, and revealed high prevalence rates of PSC in these areas [4–12]. Also recent studies consistently demonstrated that a significant increase over time in the incidence of PSC [3,7,12]. However, epidemiological data of PSC were lacking for regions of low prevalence areas, including Japan and other countries in Asia.

In Japan PSC was recognized as an uncommon liver disorder until the early 1990s, yet the number of reported cases of PSC was increasing. We conducted nationwide retrospective surveys to elucidate the characteristics of PSC in Japan in 1997 and 2003 [13,14] and demonstrated the presence of unique features of Japanese PSC patients as compared to those in patients from North America and European countries, including 2 peaks in age distribution and fewer presences of inflammatory bowel diseases as comorbidities, occurring in only 37% of PSC patients. Meanwhile, accumulating evidences, mainly originating from Japan, suggested the presence of a different clinical entity of sclerosing cholangitis with elevated serum IgG4 levels, complicated with/without autoimmune pancreatitis (AIP) [15–17]; this disorder is now defined as IgG4-related sclerosing cholangitis (IgG4-SC) [18]. In 2012, the clinical diagnostic criteria of IgG4-SC were established in Japan [19], based mainly on cholangiographic findings. It was thus possible to discriminate PSC from IgG4-SC using these criteria; therefore, we conducted the third nationwide survey to investigate the characteristics of PSC as well as IgG4-SC lacking pancreatic involvement [20]. Furthermore, we performed an epidemiological study of PSC in Japan in 2007 based on the data from national surveys and estimated the prevalence of PSC in this country [21], and as far as we know this study still remains the only epidemiological data of PSC in Asia.

In this review, first we summarized the geoepidemiological data of PSC, mainly focusing on the comparison between Europe/North America and Japan. Next, we describe the unique features of Japanese patients with PSC identified in nationwide surveys along with a focus on patients with IgG4-SC.

Abbreviations: PSC, primary sclerosing cholangitis; AIP, autoimmune pancreatitis; IgG4-SCI, gG4-related sclerosing cholangitis; IBD, inflammatory bowel diseases; CCA, cholangiocarcinoma; UC, ulcerative colitis.

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2. Geoepidemiology of PSC

To our knowledge, there have been 10 epidemiological studies indicating incidence and prevalence of PSC from 1984 to 2007, including our study [4–12,21]. The results of these studies are summarized in Table 1. The incidence rates (IR) are ranging from 0.07 to 1.3 per 100,000 inhabitants per year; almost similar IR among North America and Northern Europe, while an IR was 0.07 and exceptionally low in Spain [9]. The prevalence rate also varies, ranging from 0.22 to 16.2. In Spain a prevalence rate was the lowest, 0.22 per 100,000 inhabitants per year.

The epidemiological study conducted in Japan in 2007 was a questionnaires-based retrospective design. A questionnaire was circulated to 1910 tertiary referral centers all over in Japan, covering 43,875,000 populations of Japan. The diagnosis of PSC was made in each referral center, according to the diagnostic criteria proposed by Lindor et al. [22], mainly depending on cholangiographic studies, biochemical and histological findings, and exclusion of other possible causes. The response was obtained from 1355 centers (71%) and 415 patients with PSC were identified. Based on these figures we estimated the prevalence of PSC in Japan was 0.95 (95% CI; 0.61–1.29) [21]. Although IR was lacking in our epidemiological study, the prevalence rate of in Japan is relatively low compared to Northern Europe and North America, supporting the demographic diversity of PSC.

The difference in the prevalence of PSC between Japan and Europe/North America may be partly explained by the study design. Our study is a questionnaires-based retrospective design recruiting tertiary referral centers, not a population-based epidemiological study. As a result the number of PSC patients might be underestimated in this study by a referral or diagnostic bias. However, we sent a questionnaire to quite large numbers of tertiary referral centers all over in Japan, covering almost one-third populations of this country. Furthermore, a diagnosis of PSC is well known among gastroenterologists, and cholangiographic studies (ERCP and/or MRCP) are routinely performed in Japan. Rather, a primary factor playing a significant role in the global distribution of PSC is genetic diversity among ethnic groups. The population-based epidemiological studies in Japan and other Asian countries may help to resolve this issue.

It is of note that the incidence of PSC appears to be increasing. Recent two large cohort studies demonstrated a significant increase in IR of PSC over time [7,12]; average annual percent change (AAPC) was reported to be 3.06 (95% CI 0.01–6.20) in one study [12]. Another study also reported a tendency toward increasing incidence, although not significant [8]. Although we failed to estimate an IR in our study in Japan, the reported number of patients with PSC nearly doubled between two national surveys, 192 in 1997 [13] and 388 patients in 2003 [14]. Since a questionnaire was similarly sent to referral centers in both surveys, the increase in the number of PSC patients may reflect a real increase of IR of PSC in Japan. It remains unsolved why incidence of PSC is increasing recently. Escorsell et al. reported that although no geographical difference in incidence was found there was a trend to detect more PSC cases in industrial regions [9]. Epidemiological studies of PSC in developing countries with identical ethnic backgrounds to North America/Europe are required to solve whether this hypothesis is the case or not. Earlier diagnosis of PSC with better recognition of the disease among clinicians and better diagnostic devices may be another reason for increased IRs. However, Boonstra et al. recently demonstrated that serum bilirubin levels at diagnosis remained stable over time while incidence was rising during the same period, and denied the possibility that earlier diagnosis underlay the increase [7]. We agree this view because no significant difference in clinical profiles was noted as well between two national surveys we performed.

3. Characteristics of Japanese PSC patients as compared to those in Europe and North America

In addition to lower prevalence of PSC in Japan, we noticed several characteristic features of Japanese PSC patients in previous nationwide surveys, which had been scarcely demonstrated before by epidemiological studies from other countries. First, there were 2 peaks in the age distribution at diagnosis, i.e., in the 3rd and 7th decades of life (Fig. 1). Most previous epidemiological studies from North America and Europe indicated a single age category as the highest risk for developing PSC [23–26], except for a recent study in Canada which suggested two categories, 18–35 and >65, are higher risk groups than another categories, similar to Japanese studies [10]. Interestingly, the age distribution of PSC complicated with inflammatory bowel diseases (IBD) demonstrated a single peak in the twenties, while patients with AIP exhibited a small peak in the sixties. At this point, PSC patients with AIP are not considered to have "true" PSC, but rather are diagnosed as IgG4-SC. Although it is notable that the peak in the sixties persists even if patients with AIP are eliminated, it remains possible that IgG4-SC patients without pancreatic involvement may be misdiagnosed as PSC and thus comprise the second peak in the elderly.

Second, the prevalence of IBD as comorbidity appears to be lower in Japanese PSC patients. In various case series from North America and Northern Europe, IBD was a complication in 47–76% of PSC patients [4,6–12] (Table 2). However, in Japanese PSC patients, the presence of IBD was restricted to only 37% (125/388) patients in 2003 survey [14]. In general, total colonoscopy is frequently performed in Japanese facilities where PSC is diagnosed by endoscopic retrograde cholangiography (ERC); therefore, a lack of a thorough examination of the colon is not a plausible reason for the lower prevalence of IBD. Indeed, total colonoscopy was performed in 53%

Table 1
Incidence and prevalence of PSC.

Author [Ref.]	Country	Study period	Method of case ascertainment	No. of cases	Incidence[a] (95% CI)	Prevalence[a] (95% CI)
Escorsell et al. [9]	Spain	1984–1988	Questionnaires	43	0.07	0.22
Berdal et al. [5]	Norway	1985–1994	ICD codes	12	0.7	5.6
Boberg et al. [6]	Norway	1986–1995	Prospective cohort	17	1.3(0.8–2.1)	8.5 (2.8–14.2)
Bambna et al. [4]	US	1976–2000	Medical records linkage system	22	0.9	13.6
Card et al. [8]	UK	1987–2002	General Practice Research Database	149	0.41(0.34–0.48)	3.85 (3.04–4.80)
Kingham et al. [11]	UK	1984–2003	Prospective cohort	46	0.91	12.7
Lindkvist et al. [12]	Sweden	1992–2005	ICD codes	199	1.22	16.2
Kaplan et al. [10]	Canada	2000–2005	Retrospective cohort	49	0.92	N/A
Boonstra et al. [7]	Netherlands	2000–2007	Retrospective cohort	519	0.5	6.0
Tanaka et al. [21]	Japan	2007	Questionnaires	415	N/A	0.95 (0.61–1.29)

N/A, not available.
[a] Per 100,000 inhabitants.

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