2 Epidemiology

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Introduction

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a relatively new disease entity, thus very limited data are currently available regarding its epidemiology. To date, several case series regarding clinical profiles of IgG4-SC have been published, including our study [1–3]; however, no epidemiological studies illustrating the incidence and prevalence of IgG4-SC have been conducted. In this review, epidemiological and clinical features of IgG4-SC are discussed in general and are based mainly on data in the Japanese population.

Prevalence and Incidence

Epidemiological data on IgG4-SC is currently not available. However, it can be extrapolated from that of autoimmune pancreatitis (AIP), which is another IgG4-related disease (IgG4-RD) of the gastrointestinal system and is frequently found as a comorbid disorder in patients with IgG4-SC. In 2011, Kanno et al. carried out a clinico-epidemiological survey of AIP in Japan, yielding an overall prevalence of 4.6 per 100,000 population and an annual incidence of 1.4 per 100,000 population [4]. In that study, a prevalence of IgG4-SC in patients with AIP was reported as 39%, and thus an overall prevalence and an annual incidence of patients who have both AIP and IgG4-SC is estimated as 1.8 and 0.5 per 100,000 population, respectively. Furthermore, our nationwide survey of IgG4-SC in 2015 demonstrated that the proportion of patients diagnosed as having both IgG4-SC and AIP was 87% of all IgG4-SC cases [3]. Thus, taking both studies together, an overall incidence and an annual prevalence is calculated to be 2.1 and 0.63 per 100,000 population, respectively. These estimated incidence and prevalence in Japan are less than half of those of AIP, and the overall number of patients with IgG4-SC in Japan is estimated at 2500. The prevalence and incidence in Western countries may be different to that in Japan, thus epidemiological studies in the Japanese population are warranted.

Case Series of IgG4-SC

Biliary involvement of AIP or IgG4-RD has been already reported in 2007 [5] and is regarded as a different clinical entity from primary sclerosing cholangitis (PSC) in terms of responses to corticosteroids [6]. However, the clinical, biochemical, and radiographic features of IgG4-SC have not been well characterized, probably because of the rarity of the disease and lack of globally accepted

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T. Kamisawa, M.-H. Kim (eds.), *IgG4-Related Sclerosing Cholangitis*,
https://doi.org/10.1007/978-981-10-4548-6_2

diagnostic criteria. In 2008, Ghazale et al. analyzed the large database of AIP patients at Mayo Clinic, Minnesota, USA, and described the clinical profiles and response to therapy in 53 patients with IgG4-associated cholangitis [1]. Huggett et al. conducted the largest case series of IgG4-SC in 2014 and reported that AIP and/or IgG4-SC was associated with significant morbidity and mortality in the cohort of 115 patients, which included 68 patients with IgG4-SC [2]. In 2012, we performed a nationwide survey of PSC and IgG4-SC in Japan and described the clinical characteristics of 43 patients with IgG4-SC without AIP or "solitary IgG4-SC" [7]. In 2015, we performed another nationwide survey on PSC and IgG4-SC in Japan, which enrolled all patients with IgG4-SC, irrespective of the presence or absence of AIP [3].

It is of note that the diagnostic criteria differed among these studies. In the case series from Mayo Clinic [1], IgG4-SC was diagnosed using a combination of biliary imaging and presence of AIP. The HISORt criteria (histology, pancreatic imaging, serology, other organ involvement and response to steroid therapy) were used for confirmation of the presence of AIP. Using these criteria, four patients did not show evidence of AIP ("solitary IgG4-SC") and were histologically diagnosed as having IgG4-SC. In the case series from the UK [2], IgG4-SC was diagnosed in a similar manner, using a combination of biliary imaging and confirmation of the absence of AIP as a comorbidity. In Japan, diagnosis of AIP was made using the Japan Pancreas Society criteria initially [8] and the HISORt criteria thereafter. In our case series in Japan, the clinical diagnostic criteria established by the Japanese Biliary Association in 2012 [9] was used. While definite, probable, or possible diagnosis was established using the criteria, only patients with a definite or probable diagnosis were included.

Demographics

The demographics of patients with IgG4-SC are summarized in Table 2.1. IgG4-RD is generally a male-dominant disease, and indeed male patients are dominant in all three reports. The proportion of male patients was 85%, 74%, and 83% in the USA [1], the UK [2], and Japan [3], respectively. The age at presentation was also similar among these three reports, indicating that those in their 60s are at the highest risk for developing IgG4-SC. In Fig. 2.1, distributions of age and sex at presentation are shown in 527 cases with IgG4-SC in Japan. The age ranged from 23.0–88.5 years, and unlike PSC, which can be difficult to differentiate from IgG4-SC in terms of biliary imaging, no patient developed IgG4-SC in childhood or adolescence. The age distribution was quite similar in both male and female patients, and the median age at diagnosis was 66.2 years. Therefore, although the diagnostic criteria might differ among the three-case series, the demographics of IgG4-SC are quite comparable.

Seeking Etiological Factors

Although case-control studies for clarifying the etiology of this enigmatic disease have not been carried out, preliminary data suggested a role of environmental triggers for developing IgG4-SC and AIP [10]. A questionnaire-based study revealed that a history of blue-color work was noted in 88% of patients with IgG4-SC and/or AIP in the Amsterdam cohort and in 61% of patients with IgG4-SC and/or AIP in the Oxford cohort, both of which were much higher than that in patients with PSC. Occupational antigens such as solvents, industrial and metal dusts, and pigments

Table 2.1 Epidemiological features of IgG4-SC

Region	Year	N	Male (%)	Age at presentation (years)
USA [1]	2008	53	85	62[a]
UK [2]	2014	68	74	61[b]
Japan [3]	2017	527	83	66[b]

[a]Average
[b]Median

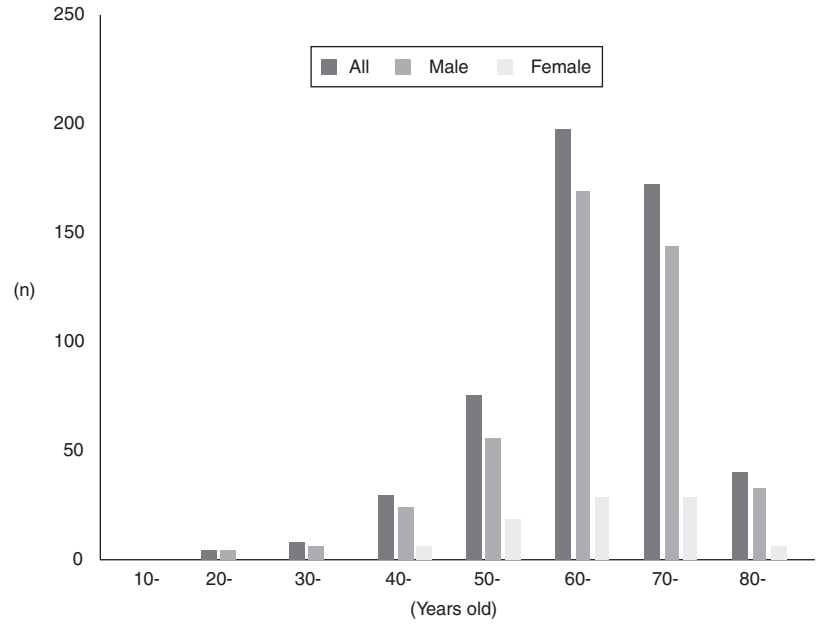

Fig. 2.1 Distribution of age at presentation, for patients with IgG4-related sclerosing cholangitis in Japan [3]

and oils, to which these patients could have been exposed, could be the triggers for developing IgG4-SC. Further investigations are warranted in other cohorts.

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