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## Introduction

Autoimmune pancreatitis (AIP) is a rare disease that has recently emerged as a unique type of pancreatitis with a presumed autoimmune etiology. In 1995, Yoshida et al. [1] proposed AIP as a diagnostic entity. They summarized the clinical features of AIP as follows: increased serum  $\gamma$ -globulin or immunoglobulin (Ig)G levels and the presence of autoantibodies; diffuse irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas; occasional association with stenosis of the lower bile duct and other autoimmune diseases; mild symptoms, usually without acute attacks of pancreatitis; effectiveness of steroid therapy; and histological findings of lymphoplasmacytic sclerosing pancreatitis (LSP) [1, 2]. Thereafter, AIP has been extensively reported worldwide including from Japan, Korea, Europe, and the United States. Because AIP is a relatively new clinical entity and the diagnostic criteria are being established, the epidemiology of AIP is not fully known. In Japan, the Research Committee of Intractable Pancreatic Disease provided by the Ministry of Health, Labour, and Welfare of Japan (RCIPD) has conducted three nationwide epidemiological surveys of AIP according to the diagnostic criteria used at that time. We here describe the epidemiology of AIP, mainly focusing on the results of nationwide surveys in Japan [3, 4].

## First Nationwide Survey of AIP in Japan

With the accumulation of similar cases in Japan, the Japan Pancreas Society (JPS) proposed the world's first clinical diagnostic criteria for AIP in 2002 [5]. The criteria consisted of 3 items: (1) specific imaging findings (a mandatory requirement), along with (2) serological and/or (3) pathological evidence. In the 2002 criteria, the length of MPD narrowing on endoscopic retrograde pancreatography (ERP) was defined as more than 1/3 of the entire pancreas to avoid confusion with short-segment narrowing or stenosis caused by pancreatic cancer. As a result, the 2002 criteria were diagnostic for the typical diffuse type of AIP but failed to diagnose the atypical localized type of AIP, which shows focal or segmental swelling of the pancreas and short-segment narrowing of MPD less than 1/3 of the entire pancreas.

Following the proposed diagnostic criteria for AIP, the RCIPD conducted the first nationwide survey of AIP in 2003 [3]. The departments of internal medicine, gastroenterology, digestive surgery, and surgery in the respective hospitals are listed, and a method of stratified random sampling was used to select the departments to be surveyed. The sampling rates were 5, 10, 20, 40, 80, 100, and 100 % for the stratum of general hospitals with less than 100 beds, 100–199 beds, 200–299 beds, 300–399 beds, 400–499 beds, 500 or more beds, and the affiliated university hospitals, respectively. In order to increase the study efficiency, some departments that were expected to treat many patients with pancreatic diseases were selected. These departments were separately classified into a “special strata” category, and all departments in this category were surveyed. A simple questionnaire was made to determine the number of patients with AIP who visited the departments in 2002. This questionnaire was directly mailed in January 2003 to the heads of 2,971 departments randomly chosen as described above. In the second-stage survey, requests for all individual patients' detailed clinico-

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epidemiological information were sent to those departments reporting that they had seen patients with AIP in 2002 in the first-stage survey.

Of 2,971 departments, 993 departments responded to the questionnaire in the first-stage survey (response rate: 33.4 %), and 294 patients with AIP were identified according to the JPS diagnostic criteria 2002. The estimated number of AIP patients in 2002 was 900 (95 % confidence interval (CI), 670–1,110), suggesting that AIP was a rare disease. In addition, 800 (95 % CI, 410–1,180) patients were suspected to have AIP, although they did not fulfill the JPS diagnostic criteria 2002. These patients might have had atypical localized type AIP, which shows focal or segmental swelling of the pancreas and short-segment narrowing of MPD less than 1/3 of the entire pancreas. Based on the second questionnaire, a total of 158 cases were confirmed to fulfill the JPS diagnostic criteria for AIP. The male to female ratio was 2.85, and the age of disease onset in 95 % of the patients was over 45 years [3].

## Second Nationwide Survey in Japan

The 2002 Criteria were revised in 2006 by the JPS and the RCIPD [6]. Major revisions included the elimination of the dependency on the length of MPD narrowing and the incorporation of IgG4 in the serology criterion. In 2001, Hamano et al. [7] reported that elevated serum IgG4 levels were highly specific and sensitive for the diagnosis of AIP. The revised diagnostic criteria consisted of characteristic radiological findings (diffuse or segmental irregular narrowing of the MPD and enlargement of the pancreas) as an essential factor in combination with serological findings (elevated serum  $\gamma$ -globulin, IgG, IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor) and/or histopathological findings (marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas) [6].

In 2008, the RCIPD started the second nationwide survey of AIP according to the revised diagnostic criteria for AIP (JPS2006) [4]. The survey was conducted in a similar manner to the first nationwide survey, and the target subjects were patients diagnosed as having AIP in 2007. The first questionnaire was directly mailed in November 2008 to the heads of 3,015 departments randomly chosen as described earlier.

Of 3,015 departments, 1,114 departments responded to the questionnaire in the first-stage survey (response

rate: 36.9 %) and 1,069 patients with AIP were identified (Table 2.1). Among them, 391 (36.6 %) cases were newly diagnosed patients as having AIP in 2007. From these data, we estimated that the total number of patients diagnosed as having AIP in Japan was 2,790 (95 % CI, 2,540–3,040), which means an estimated overall prevalence rate of 2.2 per 100,000 population. The number of patients who were newly diagnosed as AIP in 2007 was estimated to be 1,120 (95 % CI, 1,000–1,240), from which the annual incidence rate was calculated to be 0.9 per 100,000 population. The estimated number of AIP patients in this study, 2,790, was 3.1 times higher than the estimated number of 900 in the first nationwide survey in 2002 [3] and was 1.64 times higher than the 1,700 that included the number of suspected AIP patients. The rapid increase in the number of AIP may be explained by (1) the different diagnostic criteria employed in these two surveys and (2) the increasing recognition of AIP as a disease entity.

In response to the questionnaire in the second-stage survey, we collected detailed clinicoepidemiological information on 546 patients (51.0 %; 418 males, 114 females, and 14 patients of unknown sex) who had been identified by the first questionnaire. One hundred seventy-two patients were newly diagnosed in 2007, and 374 patients had been already diagnosed before 2007. All patients were Japanese. The male to female ratio of the AIP patients was 3.7. The mean age was  $63.0 \pm 11.4$  years (male/female =  $63.6 \pm 10.8/60.3 \pm 12.4$ ), and patients aged 60–69 years formed a peak in the age distribution curve (Fig. 2.1).

## Diagnosis

Imaging findings of the reported patients are summarized in Table 2.2. Approximately 90 % of the cases had enlargement of the pancreas. Among them, nearly 30 % of the cases showed localized enlargement, which was not included in the 2002 diagnostic criteria [5]. MPD narrowing was seen in more than 90 % of the cases, but narrowing was within one-third of the entire length in approximately one-third of the cases. These cases, again, did not fulfill the JPS 2002 diagnostic criteria.

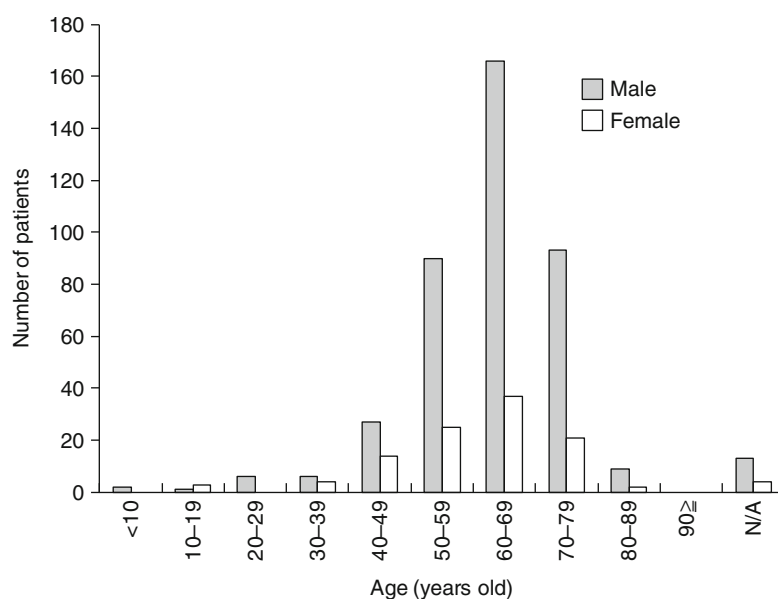
The serum IgG4 level was increased ( $\geq 135$  mg/dl) in 87.6 % of the patients (Table 2.3). The IgG level was increased in 56.9 %, but the positive rates for  $\gamma$ -globulin, antinuclear antibody, rheumatoid factor, and eosinophilia were less than half.

Tissue specimens, including both accurate and inaccurate diagnoses, were obtained from various organs including the

**Table 2.1** Patient stratification, hospital selection, and survey results

Stratification	Departments in Japan	Selection rate (%)	Departments nominated	Departments replying	Reply rate (%)	Departments replying	New cases (male/female)	Continuous cases (male/female)	Total (male/female)
Specialty hospital	80	100	80	58	72.5	58	121 (89/32)	255 (201/54)	376 (290/86)
University hospital	294	100	294	184	62.6	184	107 (84/23)	229 (186/43)	336 (270/66)
≥500 beds	679	100	679	241	35.5	241	94 (72/22)	97 (68/29)	191 (140/51)
400–499 beds	633	80	506	166	32.8	166	35 (29/6)	65 (36/29)	100 (65/35)
300–399 beds	1,156	40	462	142	30.7	142	21 (15/6)	22 (16/6)	43 (31/12)
200–299 beds	1,689	20	338	100	29.6	100	6 (4/2)	8 (6/2)	14 (10/4)
100–199 beds	3,903	10	390	128	32.8	128	5 (5/0)	0 (0/0)	5 (5/0)
≤99 beds	5,324	5	266	95	35.7	95	2 (2/0)	2 (1/1)	4 (3/1)
Total	13,758	–	3,015	1,114	36.9	1,114	391 (300/91)	678 (514/164)	1,069 (814/255)

**Fig. 2.1** Age distribution of patients with AIP in 2007 (Kanno et al. [4])



**Table 2.2** AIP-related imaging findings

Imaging	Number of cases (%)
Enlargement of the pancreas	Enlarged, 478 (87.5 %); not enlarged, 52 (9.5 %)
Area of pancreatic enlargement	Diffuse, 322 (67.4 %); localized, 141 (29.5 %)
Narrowing of the pancreatic duct	Narrowing, 468 (85.7 %); no narrowing, 40 (7.3 %)
Length of the narrowing pancreatic duct	>1/3 of 307 (65.6 %); <1/3 of 151 (32.3 %)

**Table 2.3** Serological findings in AIP patients

Serological items	Number of cases (%)
High serum $\gamma$ -globulin level ( $\geq 2.0$ g/dL)	153/381 (40.2 %)
High serum IgG level ( $\geq 1,800$ mg/dL)	292/513 (56.9 %)
High serum IgG4 level ( $\geq 135$ mg/dL)	388/443 (87.6 %)
ANA ( $\geq 80$ -fold)	154/458 (33.6 %)
RF ( $\geq 20$ )	86/315 (27.3 %)
Eosinophilia ( $\geq 8$ %)	71/388 (18.3 %)

ANA antinuclear antibody, IgG immunoglobulin G, RF rheumatic factor

pancreas in 233 (49.1 %) out of 475 cases, whereas histological examination was not performed in 242 cases (Table 2.4). Endoscopic ultrasonography-guided fine-needle aspiration was most frequently performed for obtaining pancreatic tissue samples. Pancreatic resection was performed in 51 cases on suspicion of pancreatic cancer.

Sclectrosing cholangitis was the leading extrapancreatic lesion and found in more than half of the patients (Table 2.5). Other relatively common extrapancreatic lesions included sialadenitis, lymphadenopathy, and retroperitoneal fibrosis.

Steroid was used for diagnostic purposes in 36 (6.8 %) of 530 patients. The reasons (52 in total) for steroid trial were

**Table 2.4** Histological examination performed for the diagnosis of AIP

Organs	Procedures	Number of patients <sup>a</sup>
Pancreas	Resection	51/233 (21.9 %)
	EUS-FNA	92/233 (39.5 %)
	EUS-TCB	4/233 (1.7 %)
	Percutaneous biopsy	43/233 (18.5 %)
Salivary gland	Biopsy	18/233 (7.7 %)
Bile duct	Biopsy	35/233 (15.0 %)
Duodenal papilla	Biopsy	6/233 (2.6 %)

EUS-FNA endoscopic ultrasonography-guided fine-needle aspiration, EUS-TCB endoscopic ultrasonography-guided trucut biopsy

<sup>a</sup>Including overlapping cases

**Table 2.5** Extrapancreatic lesions in the AIP patients

Extrapancreatic lesions	Number of cases (%)
Sclectrosing cholangitis	289/546 (52.9 %)
Sialadenitis	76/547 (13.9 %)
Mediastinal/abdominal lymph node swelling	69/548 (12.6 %)
Retroperitoneal fibrosis	44/543 (8.1 %)
Dacryoadenitis	36/545 (6.6 %)
Intestinal pneumonia	20/541 (3.7 %)
Chronic thyroiditis	14/538 (2.6 %)
Intestinal nephritis	14/538 (2.6 %)

as follows: the absence of characteristic imaging findings for AIP in 17 cases, negative serological findings in 19 cases, and lack of typical histological findings in 11 cases.

## Treatment

Four hundred fifty-three (83.0 %) of the 546 patients were treated with steroid, whereas the remaining 17 % patients

received no particular medication. No patients received immunosuppressants in this study. Biliary drainage was performed in 41.4 % of the patients due to obstructive jaundice in association with sclerosing cholangitis.

## Relapse

Among the 458 patients who had received steroid treatment, 134 (29.6 %) patients relapsed on imaging studies. Relapse occurred in the pancreas in 49 (36.6 %) patients, in extrapancreatic organs in 57 (42.5 %) patients, and in both the pancreas and extrapancreatic organs in 24 (17.9 %) patients.

## Third Nationwide Survey in Japan

During the 14th congress of the International Association of Pancreatology held in Fukuoka, Japan, from July 11 through 13, 2010, an international panel of experts met. The working group proposed the International Consensus Diagnostic Criteria (ICDC) [8]. AIP is classified into 2 subtypes on ICDC: type 1 related to IgG4 (LPSP) and type 2 to granulocytic epithelial lesion (idiopathic duct-centric chronic pancreatitis (IDCP)). Criteria for the two types of AIP were independently developed, and AIP is diagnosed based on one or more of the following cardinal features: imaging characteristics of the pancreatic parenchyma (P) and pancreatic duct (D), serology, other organ involvement (OOI), pancreatic histology (H), and the optional criterion of response to steroid therapy. Although the ICDC for AIP firstly enabled us to diagnose independently and compare 2 distinctive subtypes, type 1 and type 2 AIP, the ICDC system is somewhat complicated for a general use. Because cases with type 2 AIP are extremely rare in Japan, the JPS and the RCIPD revised the diagnostic criteria as the clinical diagnostic criteria for AIP 2011 (JPS2011) [9].

The RCIPD is currently conducting the third nationwide survey of AIP according to the JPS2011 diagnostic criteria. Although the details of this survey will be published elsewhere, we here briefly describe the results of the first-stage survey. The survey is being conducted in a similar manner to the previous surveys, and the target subjects are patients diagnosed as having AIP in 2011 in Japan. The first questionnaire was directly mailed in June 2012 to the heads of 4,175 departments randomly chosen as described below. By the end of November 2012, 1,875 departments responded to the questionnaire in the first-stage survey (response rate: 45.1 %), and 1,959 patients with AIP were identified. From these data, we estimated that the total number of patients diagnosed as having AIP in 2011 in Japan was 5,745 (95 % CI, 5,325–6,164), which means an estimated prevalence rate

of 4.6 per 100,000 population. The number of patients who were newly diagnosed as AIP in 2011 was estimated to be 1,808 (95 % CI, 1,597–2,018), from which the annual incidence rate was calculated to be 1.4 per 100,000 populations. The estimated number of AIP patients in this study, 5,745, was 2.1 times higher than the estimated number of 2,790 in the second nationwide survey [4].

## International AIP Surveys

The prevalence of AIP in other countries is not fully known, with reports limited to case series and description of tertiary referrals. For example, Kamisawa et al. [10] reported the clinicopathological profiles of AIP ( $n=731$ ) and the clinical profiles of LPSP ( $n=204$ ) and IDCP ( $n=64$ ) patients from 15 institutes in 8 countries. They showed that the clinical profiles of non-histologically confirmed AIP from Asia, the United States, and the United Kingdom corresponded to that of LPSP, whereas those from Italy and Germany suggested a mixture of LPSP and IDCP. Similarly, Hart et al. [11] conducted a multicenter, international analysis of patients with AIP diagnosed according to the ICDC. Twenty-three institutions from 10 different countries participated in the study, and a total of 1,064 patients fulfilling the ICDC for type 1 ( $n=978$ ) or type 2 ( $n=86$ ) AIP were included. The proportion of patients diagnosed with type 2 AIP was lower in Asian countries (3.7 %) compared with European (12.9 %,  $P<0.001$ ) and North American countries (13.7 %,  $P<0.001$ ). These studies indeed provide invaluable information about the geographical similarities and differences of AIP. Further epidemiological studies based on the universal diagnostic criteria such as ICDC would facilitate better understanding the clinicopathological characteristics of AIP worldwide.

## Summary

We reviewed the results of three nationwide epidemiological surveys of AIP in Japan. To compare the exact distribution and types of AIP worldwide, large-scale epidemiological surveys according to the universal diagnostic criteria are required.

**Acknowledgment** This work was supported in part by the Research Committee of Intractable Pancreatic Disease (principal investigator: Tooru Shimosegawa) provided by the Ministry of Health, Labour, and Welfare of Japan.

## Disclosure

All authors disclosed no financial relationships relevant to this publication.

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