Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden

Miroslav Vujasinovic[1], Roberto Valente[1,7], Pia Maier[1], Victoria von Beckerath[1], Stephan L. Haas[1], Urban Arnelo[1], Marco Del Chiaro[1], Nikolaos Kartalis[2,4], Raffaella Maria Pozzi-Mucelli[2,4], Carlos Fernandez-Moro[3], Caroline Sophie Verbeke[3,5], Jingru Yu[6], Weimin Ye[6] and J.-Matthias Löhr[1,4]

[1]Department for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Abdominal Radiology, Karolinska University Hospital, Stockholm, Sweden

[3]Department of Pathology, Karolinska University Hospital, Stockholm, Sweden

[4]Department of Clinical Science, Intervention, and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden

[5]Department of Pathology, University of Oslo, Oslo, Norway

[6]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

[7]Department for Digestive Diseases, Sapienza University of Rome, Rome, Italy

Corresponding author:
J.-Matthias Löhr, MD, PhD
Professor of Gastroenterology and Hepatology
Karolinska Institute, CLINTEC
Department for Digestive Diseases
Karolinska University Hospital
SE-141 86 Stockholm
Tel.: +46 8 5858-9591
Fax.: +46 8 5858-2340
E-mail: matthias.lohr@ki.se

Abstract:

Introduction: Autoimmune pancreatitis (AIP) is a pancreatic inflammatory process characterized by a strong inflammatory cell infiltration and two histopathologically distinct subtypes: type 1 and type 2. Diagnosis is often challenging and requires a combination of clinical, laboratory and imaging data. AIP can mimic pancreatic tumours leading to unnecessary resections if not correctly diagnosed. Short- and long-term outcomes of AIP have been poorly investigated so far and no large series have been previously reported from Sweden.

Methods: A single-centre, retrospective, cohort study of patients with histologically confirmed or highly probable diagnosis of AIP according to ICDC criteria. Demographic, clinical and radiological characteristics, type of treatment and its outcomes were collected and analysed.

Results: Seventy-one patients with AIP (87% with type 1), were evaluated at Karolinska University Hospital between 2004 and 2018; 49% males, mean age 49 years (range 44–53). Among them, 28% were histologically confirmed, 35% presented with jaundice, 22% with acute pancreatitis, 39% had non-specific symptoms such as weight loss or abdominal pain, 84% showed other organ involvement (OOI). Radiologically, 76% showed a focal pancreatic enlargement, 27% diffuse enlargement, 27% signs of acute pancreatitis and 10% of chronic pancreatitis.

Overall, 58 patients (81%) underwent treatment with different medications: 46 (79%) cortisone, 7 (12%) azathioprine, 5 (8%) other immunosuppressive drugs. Twenty-six (36%) underwent biliary stenting and 12 (16%) were given surgery.

In total, 47% of patients developed pancreatic exocrine insufficiency (PEI), of whom 76% had a severe form (faecal elastase-1 < 100 µg/g) and 21% of patients developed diabetes mellitus (pancreatic endocrine insufficiency), of whom 73% required insulin.

Conclusions: AIP is a challenging disease for diagnosis and treatment. Cortisone treatment is generally successful and provides clinical remission in the large majority of patients (>90%). In the further course of the disease, a considerable number of patients develop PEI and diabetes. Only one-quarter of patients exhibit on imaging the characteristic “sausage-like”

pancreas (diffuse enlargement), approximately three-quarters had a focal mass that could be misdiagnosed as pancreatic malignancy.

Key words: autoimmune, pancreatitis, chronic, pancreatitis, immunoglobulin G4

Introduction

Autoimmune pancreatitis (AIP) is a special form of chronic pancreatitis with a strong lymphocytic infiltration as the pathological hallmark and two histopathologically distinct subtypes: a lymphoplasmacytic sclerosing pancreatitis (LPSP, AIP type 1) and idiopathic duct-centric pancreatitis (IDCP, AIP type 2) [1]. Estimated prevalence of AIP is 4.6 per 100,000 inhabitants [2, 3].

The disease was first described by Sarles in 1961 [4] and named AIP in 1995 when clinicopathological similarities to autoimmune hepatitis were noticed [5]. Diagnosis of AIP is not always straightforward and requires a combination of different clinical, laboratory and imaging data. Over the last two decades, many diagnostic criteria for AIP have been proposed in the literature [6-10]. According to the International Consensus Diagnostic Criteria (ICDC 2010), the diagnosis of AIP is based on the presence of one or more of the following factors: pancreatic parenchyma and pancreatic duct imaging, serum IgG4 level, other organ involvement, histology of the pancreas and response to steroid treatment [11].

Over the past decade, several European case studies of AIP have been published [12-20] but none of them reported on Scandinavia, a European area suffering from a high prevalence of sclerosing cholangitis and autoimmune hepatitis, which could represent the hepatic counterpart of autoimmune pancreatitis [21, 22].

So far, very few studies have investigated short- and long-term outcomes (such as diabetes and exocrine pancreatic insufficiency), and none of these were in Scandinavian populations. The aim of the present study was to determine clinical presentations, and short and long-term outcomes of AIP in Scandinavia. as well as to identify possible risk factors predictive for pancreatic endocrine and exocrine insufficiency.

Patients and methods

Study design: We performed a single-centre retrospective study on a prospectively collected cohort of patients seen at the outpatient clinic of the Department of Digestive Diseases at Karolinska University Hospital in Stockholm, Sweden between 2004 and 2017.

Cohort: Consecutive patients with histologically proven or highly probable diagnosis according to ICDC (retrospective analysis and diagnosis according to ICDC criteria was performed for patients diagnosed during the period before the publication of ICDC [11]. All patients were discussed in the setting of a multidisciplinary conference and classified as having type 1 or type 2 AIP according to clinical, radiological and/or histological features.

Demographic, clinical and radiological characteristics (symptoms, other organ involvement, lab value) were collected. The imaging features at CT and/or MRI were defined as either a diffuse (so-called "sausage-like pattern") or focal swelling of the pancreatic gland, with reduced contrast enhancement in the pancreatic arterial phase, delayed enhancement in the venous and late phase and eventually a peripheral rim enhancement [23]. The presence of changes in the main pancreatic duct (MPD), such as long and/or multiple strictures or focal stenosis without significant upstream dilatation were also recorded [24].

Type of treatment, and short- and long-term outcomes (development of cancer, exocrine/endocrine function) were also collected.

Diagnostic delay was defined as the period from the beginning of the first symptoms to the AIP diagnosis. Follow-up period was defined as the period from AIP diagnosis until death or the last visit. Other organ involvement (OOI) was defined as the presence of extra-pancreatic disease. Normal serum IgG4 levels were recognized as those below the upper limit of normal for our laboratory (reference level 0.05–1.25g/L). Remission was defined as the disappearance of symptoms and imaging manifestations after the initial treatment. Relapse was defined as the recurrence of symptoms of AIP after initial resolution and/or radiological manifestations in the pancreas or extra-pancreatic organs after exclusion of other diseases [20].

Pancreatic exocrine insufficiency (PEI) was defined by low faecal elastase (<200µg/g).

Statistical methods:

Differences between type 1 AIP group and type 2 AIP group were evaluated using a Chi-square test or Fisher's exact test for categorical variables and the Wilcoxon Two-Sample test for continuous variables. Values were represented as the mean ± standard deviation, and *p*

values of less than 0.05 were regarded as being statistically significant. Analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

Ethics:

The study was approved by the Clinic Ethical Committee in Stockholm (2016/1571-31) and complies with the Declaration of Helsinki.

Results

Seventy-one patients with AIP were evaluated at Karolinska University Hospital between 2004 and 2018; 49% males, mean age 49 years (44–53). IgG4 was elevated in 27 out of 62 (43.5%) patients with type 1 AIP and in 0 (0%) of patients with type 2 AIP (p value=0.01). In 20 (28%) patients AIP was histologically confirmed. AIP was definitively diagnosed in 52 (73%) and probable in 19 (27%) patients. Patients' characteristics are summarized in Table 1.

Symptoms:

Twenty-five patients (35%) presented with jaundice, 16 (22%) with acute pancreatitis, 28 (39%) with non-specific symptoms such as weight loss or abdominal pain which did not fulfil the criteria for acute pancreatitis; 60 patients (84%) showed other organ involvement (OOI) including one or a combination of the following: cholangitis (n=47), nephritis (n=13), inflammatory bowel disease (n=11), autoimmune hepatitis (n=4), retroperitoneal fibrosis (n=3), sialo adenitis (n=3), autoimmune thyroiditis (n=3), vasculitis (n=4), dacryoadenitis (n=2), duodenal papilla IgG4 involvement (n=2), lung involvement (n=1), mediastinal lymph node swelling (n=1) and abdominal lymph node swelling (n=1). Other unrelated autoimmune disorders were also present, such as rheumatic polymyalgia (n=2), Sjögren's syndrome (n=1), coeliac disease (n=1), psoriasis (n=1), autoimmune haemolytic anaemia (n=1) and autoimmune gastritis (n=1).

Radiological features at diagnosis:

Radiologically, 53 patients (76%) displayed a focal pancreatic enlargement, 19 patients (27%) diffuse enlargement, 19 (27%) signs of acute pancreatitis and 7 (10%) associated signs of chronic pancreatitis.

Treatment and outcomes:

In total, 58 patients (81%) underwent treatment, of whom 46 (79%) had cortisone, 7 (12%) azathioprine, 2 (3%) mycophenolate mofetil, 1 (1%) cyclosporine, 1 (1%) rituximab (patient with rheumatoid disease) and 1 (1%) vedolizumab (patient with inflammatory bowel disease). Twenty-six (36%) patients underwent biliary stenting because of a stricture and 12 (16%) underwent surgery.

All patients treated with cortisone showed a clinical response. After a median follow up of 46 months, 97% of patients were still alive, 92% were in clinical remission, 70% had a radiologically complete response and 89% were treatment-free. Nine patients (12%) were on a tapering dose of steroids or a low-maintenance dose (5–10 mg) at the time of analysis. None developed pancreatic cancer but one patient (1%) developed a mucinous cystic neoplasm (MCN) with high-grade dysplasia and underwent successful surgical resection. Two patients had died due to extra-pancreatic diseases.

Pancreatic exocrine and endocrine insufficiency:

In total, 47% of patients developed pancreatic exocrine insufficiency (PEI), of whom 76% had a severe form (faecal elastase-1 < 100 µg/g). Fifteen (21%) patients developed diabetes mellitus (pancreatic endocrine insufficiency), of whom 11 (73%) required insulin. Short- and long-term outcomes are presented in Figure 1.

Discussion

The aim of the present study was to determine, according to ICDC, the diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden. This is the first Swedish study and the largest study on AIP in the Scandinavian countries. Autoimmune pancreatitis is an enigmatic disease and sometimes difficult to diagnose. This, in part, is responsible for the sparse data currently available on the epidemiology [25] and natural course of the disease across the world. In addition, significant differences in the clinical presentation and the relation between AIP type 1 and AIP type 2 seem to exist. It is therefore of clinical importance to draw a global picture of the disease.

Our findings show that AIP type 1 is the more frequent form of AIP (87%) and that cases are balanced by gender (female 51%) compared to European and Spanish studies (male/female ratio 2:1 and 2.75:1, respectively) [19, 20]. Acute pancreatitis, obstructive jaundice and non-specific symptoms like weight loss or abdominal pain were the predominant symptoms at the time of presentation, as observed in other studies [17, 20].

Diagnostic delay, defined as the interval between the first symptoms and time of diagnosis, was 6 months in type 1 AIP and 7 months in type 2 AIP, which is shorter than reported in the Spanish study [20] (36 weeks in AIP type 1 and 54 weeks in AIP type 2). In other studies, diagnostic delay was not defined [12, 17, 19, 26].

In some European studies, patient series were not analysed separately for AIP type 1 and AIP type 2, hence a direct comparison of statistical analysis according to ICDC was not possible [12, 14, 15, 17]. Before the ICDC was achieved, Unifying-Autoimmune-Pancreatitis-Criteria (U-AIP) to diagnose AIP were developed [27]. The same group of authors recently proposed the M-ANNHEIM-AiP-Activity-Score (MAAS), which was successfully validated in their own and an external patient cohort [28]. During the period before ICDC, other national and institutional sets of diagnostic criteria, e.g. the Japanese [8], Korean [29], Asian [10], Mayo-HISORt [7], and Italian diagnostic criteria represented the standard of care [12]. Limitations to previous criteria include the restriction to IgG4-associated disease and the exclusion of possible diagnostic features such as the presence of other autoimmune diseases or the response to immunosuppressive medication [27]. Several studies have retrospectively tested ICDC and confirmed its superiority compared to the previously published systems [30-32].

Other organ involvement (OOI) in AIP type 1 patients in Sweden was present in 84% of patients. This is higher than the rates reported by other European studies, which varied from 47% to 61% [12, 15, 17, 20].

IgG4 was elevated in 27 out of 62 (43.5%) patients with type 1 AIP, which is lower than in other studies (50–82%) [12, 15, 17, 19]. The differences can be explained by the characteristics of the included patients (27% with probable AIP according to ICDC in our study).

Pancreatic exocrine insufficiency (PEI) at the time of analysis was present in 47% of patients. The occurrence of PEI ranged from 36% to 60% in other studies [14, 15]. A cross-sectional study of patients with alcoholic and idiopathic chronic pancreatitis suggests that PEI is considerably more widespread than is generally assumed [33]. A recently published study

from a Spanish group showed an increased risk of mortality associated with PEI in patients with chronic pancreatitis [34]. Chronic pancreatitis has been associated with an increased risk of pancreatic cancer [35]. In addition, autoimmune diseases have been associated with increased carcinogenic risk [36]. Recently published experiences from Germany confirmed that the incidence of malignant disease in patients with AIP is significantly increased compared to the general population [37]. In our study, during the follow-up period of 46 months, no pancreatic cancer was diagnosed but one patient developed mucinous cystic neoplasia (MCN) with high-grade dysplasia which was successfully treated surgically.

Diabetes mellitus (DM) was present in 21% of patients at the time of data analysis. Occurrence of DM ranged from 12% to 55% in other studies [12, 15, 17, 20].

AIP is a treatable form of chronic pancreatitis with a good response to steroid therapy [25]. The response to initial steroid therapy was excellent in this study (100%), but relapses occurred in 27% of all patients. Relapse occurrence in other European studies varied from 7 to 55% [12, 14, 15, 17]. Although there is general agreement that steroids are the ideal initial treatment, there is no clear consensus regarding the treatment for disease relapses [25]. In total, 58 patients (81%) underwent treatment with different medications: 46 (79%) cortisone, 7 (12%) azathioprine, 5 (8%) other immunosuppressive drugs. Twenty-six patients (36%) underwent biliary stenting and 12 (16%) were given surgery.

After a median follow up of 46 months, 97% of patients were still alive, 92% were in clinical remission, 70% displayed a radiologically complete response, and 89% were treatment-free.

Conclusion

AIP type 1 is the dominant form of the disease in Sweden and most commonly presents with abdominal pain, obstructive jaundice and weight loss. Cortisone treatment is generally successful and provides clinical remission in the large majority of patients. In the further course of the disease, a considerable number of patients develop PEI and diabetes. Only one-quarter of patients exhibit the characteristic diffuse enlargement (“sausage-like” pancreas).

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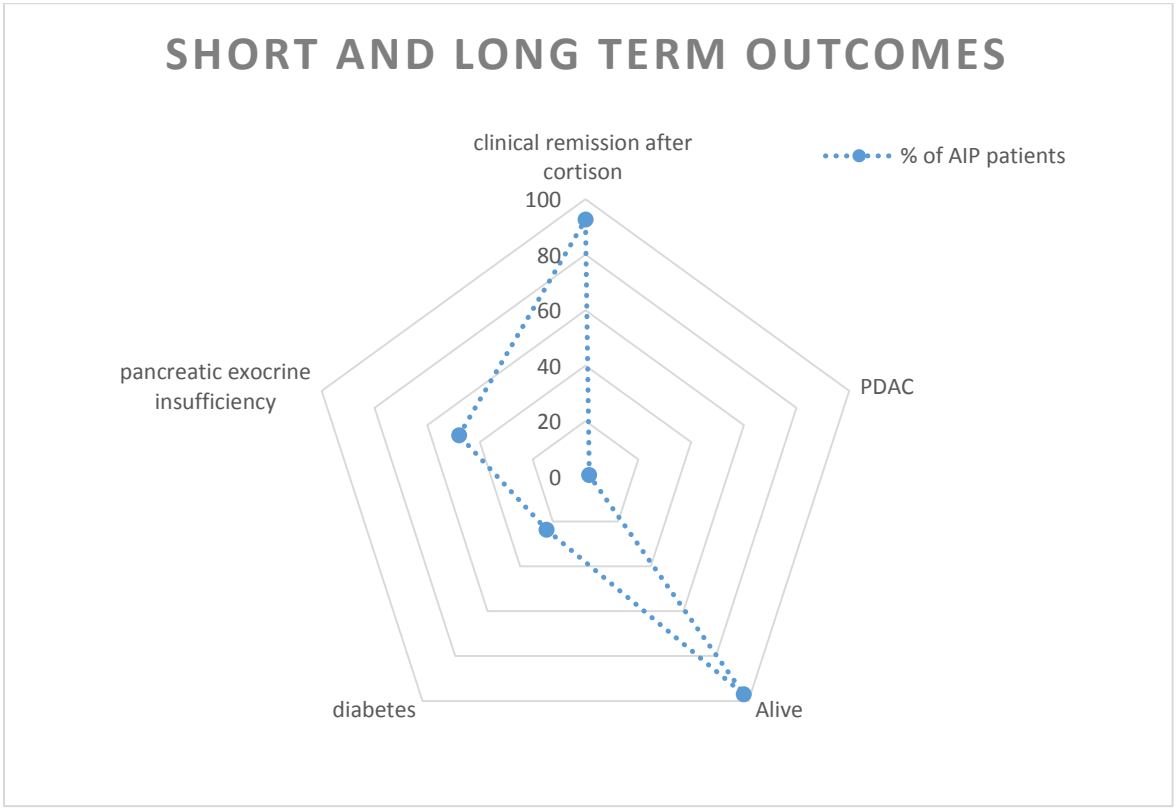
Tables and figures:

Figure 1. Graph showing short and long-term outcomes of AIP in Sweden



AIP=autoimmune pancreatitis; PDAC=pancreatic ductal adenocarcinoma

Table 1. Clinical features and differences between types 1 and 2 AIP.

Parameters	Type 1 AIP (n=62)	Type 2 AIP (n=9)	Total (n=71)	P-value
Age at diagnosis (Mean±SD, years)	49.6 ± 18.7	46.9 ± 22.2	49.3 ± 19.0	0.42[W]
Age at analysis (Mean±SD, years)	53.5 ± 19.9	49.7 ± 22.7	53.0 ± 20.1	0.83[W]
Diagnostic delay (Mean±SD, months)	6.3 ± 12.8	7.0 ± 10.5	6.4 ± 12.5	0.71[W]
Sex (n, %)				0.48[F]
Female	30 (48.4)	6 (66.7)	36 (50.7)	
Male	32 (51.6)	3 (33.3)	35 (49.3)	
Relapses (n, %)				0.10[F]
Elevated IgG4	27 (43.5)	0 (0)	27 (38.0)	0.01 [F]
No	42 (68.9)	9 (100)	51 (72.9)	
Yes	19 (31.2)	0 (0)	19 (27.1)	
Missing	1			
Pancreatic Exocrine Insufficiency (n, %)				0.04[F]*
No	16 (25.8)	4 (44.4)	20 (28.2)	
Yes	33 (53.2)	1 (11.1)	34 (47.9)	
Missing	13 (21.0)	4 (44.4)	17 (23.9)	
Diabetes Mellitus (n, %)				0.40[F]
No	42 (67.7)	6 (66.7)	48 (67.6)	
Yes	14 (22.6)	1 (11.1)	15 (21.1)	
Missing	6 (9.7)	2 (22.2)	8 (11.3)	

W, Wilcoxon Two-Sample test; F, Fisher's exact test. *, P<0.05.