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Kanie, Keitaro ; Bando, Hironori ; Iguchi, Genzo ; Shiomi, Hideyuki ; Masuda, Atsuhiko ; Fukuoka, Hidenori ; Nishizawa, Hitoshi ; Fujita,...

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Corresponding Author:	Yutaka Takahashi, M.D., P h .D. Kobe University Graduate School of Medicine Kobe, JAPAN	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	Kobe University Graduate School of Medicine	
Corresponding Author's Secondary Institution:		
First Author:	Keitaro Kanie	
First Author Secondary Information:		
Order of Authors:	Keitaro Kanie	
	Hironori Bando	
	Genzo Iguchi	
	Hideyuki Shiomi	
	Atsuhiko Masuda	
	Hidenori Fukuoka	
	Hitoshi Nishizawa	
	Yasunori Fujita	
	Arata Sakai	
	Takashi Kobayashi	
	Yuuki Shiomi	
	Kenichi Yoshida	
	Ryusaku Matsumoto	
	Kentaro Suda	
	Yuzo Kodama	
	Wataru Ogawa	
	Yutaka Takahashi, M.D., P h .D.	
Order of Authors Secondary Information:		
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IgG4-related hypophysitis in patients with autoimmune pancreatitis

Keitaro Kanie^{1,4}, Hironori Bando^{1,4}, Genzo Iguchi², Hideyuki Shiomi³, Atsuhiko Masuda³, Hidenori Fukuoka², Hitoshi Nishizawa¹, Yasunori Fujita¹, Arata Sakai³, Takashi Kobayashi³, Yuuki Shiomi³, Kenichi Yoshida¹, Ryusaku Matsumoto¹, Kentaro Suda¹, Yuzo Kodama³, Wataru Ogawa¹, and Yutaka Takahashi¹

¹Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine

²Division of Diabetes and Endocrinology, Kobe University Hospital

³Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine

⁴These authors equally contributed to this work.

Address all correspondence and requests for reprints to Yutaka Takahashi, Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. E-mail: takahash@med.kobe-u.ac.jp

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Abstract

Purpose: IgG4-related disease involves various organs including the pituitary and pancreas. The prevalence of IgG4-related hypophysitis is relatively rare compared with IgG4-related pancreatitis (autoimmune pancreatitis). Although several cases demonstrating both autoimmune pancreatitis and hypophysitis have been reported, the prevalence of IgG4-related hypophysitis in patients with autoimmune pancreatitis remains unknown. This study aimed at screening for IgG4-related hypophysitis to accurately determine its prevalence in patients with autoimmune pancreatitis.

Methods: In this cohort study, we screened IgG4-related hypophysitis via pituitary magnetic resonance imaging (MRI) and endocrinological examination in 27 patients who were undergoing follow-up for autoimmune pancreatitis at Kobe University Hospital between 2014 and 2018.

Results: Among 27 patients with autoimmune pancreatitis, 5 patients exhibited morphological abnormalities in the pituitary (18.5%). Among them, one patient (3.7%) met the criteria for hypophysitis with an enlarged pituitary and stalk concomitant with hypopituitarism. After glucocorticoid treatment, the enlarged pituitary shrank and became empty sella during the clinical course. Four patients (14.8%) revealed empty sella without obvious pituitary dysfunction. Four of 5 patients with morphological pituitary abnormalities showed multiple organ involvement in addition to pancreatic and pituitary involvement. Accordingly, multiple organ involvement was more prevalent in patients with morphological pituitary abnormalities (80%) compared to those without (48%).

Conclusions: Although a large-scale study is necessary to validate these results, these data suggest that the prevalence of hypophysitis in patients with autoimmune pancreatitis may be underestimated. Based on our findings, we recommend screening for hypophysitis, especially in patients with multiple organ involvement.

Introduction

Immunoglobulin G (IgG) 4-related disease (RD) is a well-recognized clinical entity that was first proposed following the observation of patients with autoimmune pancreatitis in 2001 [1]. This disease involves various tissues and is associated with several conditions, such as Mikulicz's disease, autoimmune pancreatitis, Riedel's thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, inflammatory pseudotumor, and hypophysitis [2]. In IgG4-RD, many patients have lesions in multiple organs, either synchronously or metachronously, and others show single organ involvement [3]. The incidence of this disease was estimated to be 0.28-1.08/100,000 patients [4]. Among all IgG4-related diseases, the organ-specific diagnostic criteria for autoimmune pancreatitis have been well-defined.

IgG4-related hypophysitis is an IgG4-RD, which was initially reported in 2004 [5]. Leporati et al. first proposed the diagnostic criteria for IgG4-related hypophysitis in 2011 [6]. The majority of cases of IgG4-related hypophysitis were observed in middle-aged to elderly men, similar to other IgG4-RDs [7]. IgG4-related hypophysitis presents with various degrees of hypopituitarism and diabetes insipidus (DI) with a thickened pituitary stalk and/or pituitary mass. IgG4-related hypophysitis was noted in 30% of hypophysitis and 4% of all hypopituitarism/DI cases [8]. Recently, it has been reported that 14.3% of patients with IgG4-related hypophysitis also had autoimmune pancreatitis [9], suggesting a complication of hypophysitis and autoimmune pancreatitis may be not rare; however, the prevalence of hypophysitis in patients with autoimmune pancreatitis has not been clarified. This is important because autoimmune pancreatitis is not a rare disease.

Although the clinical symptoms of hypopituitarism are usually nonspecific, it is important that hypopituitarism is accurately diagnosed as it can potentially lead to increased mortality because of adrenal crisis, but notably most patients may be treated with glucocorticoids [10]. In addition, IgG4-related hypophysitis with pituitary enlargement and bitemporal hemianopsia without hypopituitarism has been reported [11]. An enlarged pituitary gland may cause symptoms, such as headaches and loss of vision. Therefore, it is important to pay attention to the possibility of accompanying hypophysitis in patients with IgG4-RD.

In this cohort study, we aimed at screening for IgG4-related hypophysitis via pituitary magnetic resonance imaging (MRI) and endocrinological examination in patients who had been undergoing follow-up for autoimmune pancreatitis to accurately determine the prevalence of the condition. A review of the current literature is also provided.

Subjects and Methods

Subjects

This study was approved by the ethics committee of Kobe University Graduate School of Medicine and all the subjects provided written informed consent for the analysis. We screened 27 patients with autoimmune pancreatitis followed in Kobe University Hospital (Figure 1). The diagnosis of autoimmune pancreatitis was based on the clinical diagnostic criteria of autoimmune pancreatitis [12](Supplementary Table 1). Autoimmune pancreatitis was comprehensively diagnosed [12], in patients presenting with obstructive jaundice or pancreatic enlargement/mass, with denial of malignant disease, based on the results of pancreatic image, blood test, histopathological findings, a presence of extra-pancreatic lesions, and response to the steroid therapy [12, 13]. All cases were diagnosed as type 1 autoimmune pancreatitis.

For the screening of hypopituitarism, we measured basal levels of pituitary hormones and peripheral hormones [10]. In patients with suspicion of hypopituitarism and/or those with evidence of pituitary abnormality on MRI, further endocrinological examinations including hormone provocation tests were performed to obtain a definitive diagnosis [10, 14–17]. Provocative test for the evaluation of the pituitary function was performed by using insulin (0.05 unit/kg), TRH (200 µg), LHRH (100 µg). The diagnosis of IgG4-related hypophysitis was made according to existing diagnostic criteria as previously described [6].

Serum IgG4 Measurement

Serum IgG4 concentrations were measured using IgG4 (BS-NIA) kits (The Binding Site, Birmingham, UK). The normal value of IgG4 ranges from 5-105 mg/dL. The criterion of IgG4 levels in IgG4-RD were defined as more than 135 mg/dL [3, 12].

Statistical analysis

Data are expressed as means ± standard deviations or medians [interquartile range]. Statistical analyses were performed using JMP Statistical Database Software version 12.2.0 (SAS Institute, Cary, NC).

Results

The prevalence of hypopituitarism and pituitary abnormalities in autoimmune pancreatitis cases

Clinical characteristics of the 27 patients (22 males (81.5%) and 5 females (18.5%)) with autoimmune pancreatitis are shown in Table 1. Twenty-two cases were diagnosed histologically with autoimmune pancreatitis by biopsy specimen. The age of onset of IgG4-RD and autoimmune pancreatitis were 63.4 ± 12.1 and 64.5 ± 11.8 years, respectively. The middle-aged to elderly male predominance of this cohort study was comparable with previous reports [18]. Twenty-two cases were under steroid treatment at the time of screening for pituitary. Thirteen out of 27 cases (48.1%, 7 salivary glands, 6 kidney, 4 lacrimal glands and retroperitoneum, 2 aorta and lymph node, and 1 duodenum) showed other organ involvement in addition to autoimmune pancreatitis. Five patients (18.5%) revealed abnormalities in pituitary MRI. Among them, 1 patient (3.7%) showed pituitary enlargement with a thickened stalk (Figure 2) and was diagnosed with hypopituitarism and the other 4 cases showed empty sella (Figure 3). The clinical history of case 1 is described in detail below.

Case 1: A 66-year-old man was diagnosed with Mikulicz's disease and treated with glucocorticoid (30 mg/day). At that time, serum IgG4 concentration was markedly elevated at 802 mg/dL (normal range 5–105 mg/dL). At the age of 68 years, autoimmune pancreatitis, retroperitoneal fibrosis, and IgG4-related kidney diseases were diagnosed. At the age of 78 years, we detected pituitary abnormalities on MRI and endocrinological examination revealed a presence of hypopituitarism (Table 2). Hydrocortisone (10 mg/day) and levothyroxine (25 µg/day) replacement therapy were started and the enlarged pituitary shrank within 1 month; however, pituitary function was not restored thereafter (data not shown). Although pituitary biopsy was not performed, the pituitary MRI findings, the presence of biopsy-proven diagnosis of autoimmune pancreatitis, and elevated serum IgG4 level lead the diagnosis of IgG4-related hypophysitis [6] based on the criteria for IgG4-RD.

Additionally, 4 patients (cases 2–5) were diagnosed with empty sella based on MRI findings (Figure 3), which is frequently observed in the late stage of hypophysitis [19, 20]. These patients with empty sella had no evidence of impaired anterior pituitary function at the time of screening. Interestingly, case 2, who presented with autoimmune pancreatitis at the age of 76 years old, demonstrated transient central hypothyroidism (TSH 1.968 µIU/ L (reference range: 0.449–3.809 µIU/ L) and FT4 0.73 ng/ dL (0.82–1.22 ng/ dL)) 3 years before the onset of autoimmune pancreatitis when he had not treated with glucocorticoid. Although pituitary MRI was not performed at that time, it is suggested that this case might have developed hypophysitis at that time.

Relationship between other organ involvement and pituitary abnormalities

In this cohort, we have detected 5 patients (18.5%) with morphological pituitary abnormalities among a cohort of 27 patients with autoimmune pancreatitis. Interestingly, 4 cases (80%) showed multiple organ involvement including a autoimmune pancreatitis (Table 3). In contrast, 41% of autoimmune pancreatitis patients without morphological pituitary abnormalities showed multiple organ involvement, suggesting that pituitary involvement is associated with susceptibility of multiple organ involvement.

Discussion

In this cohort study, we screened for the presence of hypophysitis in 27 patients with autoimmune pancreatitis and identified 5 patients (18.5%) with pituitary MRI abnormalities and 1 patient (3.7%) was diagnosed with typical hypophysitis accompanied with hypopituitarism. It has been reported that the prevalence of IgG4-related hypophysitis was 1.7% among 118 cases of IgG4-RD including autoimmune pancreatitis [21]; however there have been no reports regarding the prevalence of IgG4-related hypophysitis in patients with autoimmune pancreatitis. Our data suggest that the involvement of the pituitary gland in patients with autoimmune pancreatitis may be underestimated.

To the best of our knowledge, 12 cases of IgG4-related hypophysitis concomitant with autoimmune pancreatitis have been reported including the present case [5, 8, 22–29] (Table 4). The ages (mean $\pm$ SD) at the time of onset of IgG4-RD, autoimmune pancreatitis, and hypophysitis were 64.2 ± 10.5 , 64.5 ± 10.3 , and 68.8 ± 8.6 years, respectively. The median of the duration from the onset of autoimmune pancreatitis to the onset of hypophysitis was 2.5 years [0, 8]. Ten out of 12 cases (83.3%) of IgG4-related hypophysitis with autoimmune pancreatitis showed the other lesions. Retroperitoneum and lung were the most common organs (5 cases, 42%), followed by the salivary glands (4 cases, 33%), kidney and lymph node (2 cases, 17%), and gallbladder, choroid plexus, and aorta (1 case, 8%).

In our cohort study, 4 out of 27 cases (14.8%) revealed empty sella without pituitary dysfunction. The case with hypophysitis (case 1) initially showed swelling of the anterior pituitary and a thickened stalk, but then the patient suffered from pituitary atrophy during the course of hydrocortisone treatment. Including this case, 5 out of 27 cases (18.5%) showed empty sella during their clinical course. Given that the prevalence of empty sella on routine MRI was 1.9% (241 out of 12,414 subjects) [30], and therefore the prevalence of 18.5% in our study is very high. It has been observed that empty sella occurred after glucocorticoid treatment in IgG4-related hypophysitis and lymphocytic hypophysitis [19]. Furthermore, it has been reported that glucocorticoid therapy improved pituitary function and reduced serum IgG4 levels [26], up to 40% [31]. Taken together, it is speculated that the 4 cases with empty sella may be a result of hypophysitis but steroid therapy for autoimmune pancreatitis was efficacious in maintaining pituitary function and preventing hypopituitarism.

The majority of the patients in our cohort received glucocorticoid treatment. Therefore, the evaluation of the hypothalamus-pituitary-adrenal axis is difficult and there is a possibility that isolated ACTH deficiency may be overlooked [32]. Generally, the majority of IgG4-related hypophysitis demonstrates combined hypopituitarism and/or central diabetes insipidus, and isolated ACTH deficiency is rare [7, 8]. In this study, the patients with hypophysitis

(case 1) showed a panhypopituitarism that was a typical pattern of hormone deficiency [7, 8].

At present, there are no predictive markers for pituitary involvement in autoimmune pancreatitis or IgG4-RD. Generally, patients with autoimmune pancreatitis or IgG4-RD are treated with glucocorticoids, and steroid therapy may mask the manifestation of central adrenal insufficiency associated with hypophysitis, therefore making clinical diagnosis of hypophysitis difficult. In this study, we demonstrated that patients with multiple organ involvement including autoimmune pancreatitis have a higher incidence of hypophysitis. Thus, we recommended evaluation of pituitary and peripheral hormone levels in patients with multiple organ involvement.

Although further large-scale studies are necessary to validate the present results, these data suggest that the prevalence of hypophysitis in patients with autoimmune pancreatitis may be underestimated. Therefore, we recommend that clinicians screen for hypophysitis, especially in patients with multiple organ involvement.

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Author contributions

K.K, H.B, and G.I performed analysis and interpretation of data and wrote the draft of the article. H.S, A.M, A.S, T.K, Y.S, and Y.K contributed to the preparation of the patient cohort. H.F, H.N, K.Y, R.M, K.S, and W.O contributed to the assembly of data. Y.T contributed to the study supervision and critical revision of the article for important intellectual content.

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Conflict of Interest

The authors declare no conflict of interest associated with this research.

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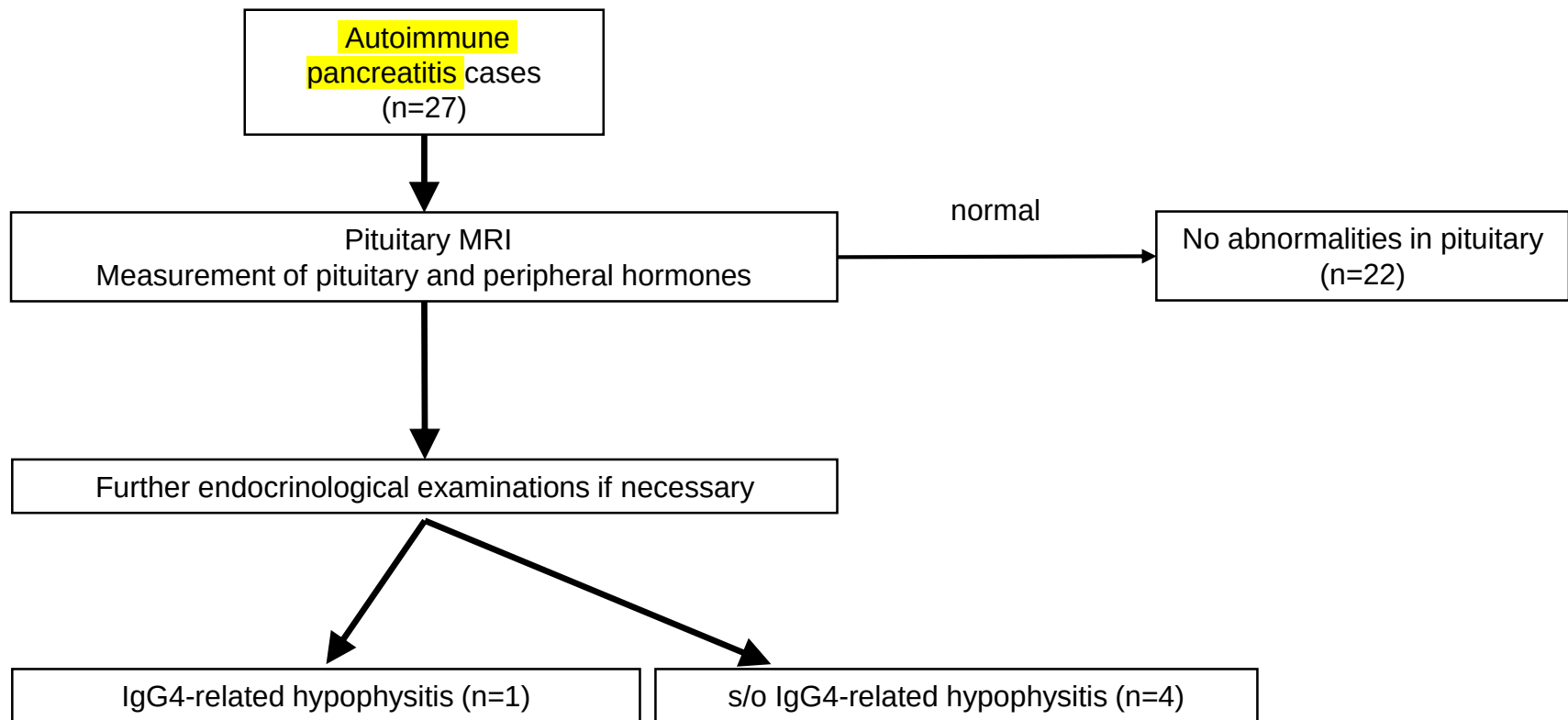
Figure legends

Figure 1. Study design of the screening for IgG4-related hypophysitis.

Figure 2. Changes in the pituitary MRI findings of case 1 that showed a typical IgG4-related hypophysitis.

Enlargement of the pituitary gland and thickened pituitary stalk shrank and became empty sella during the glucocorticoid treatment.

Figure 3. Pituitary MRI findings of 4 cases that showed empty sella.



Case 1



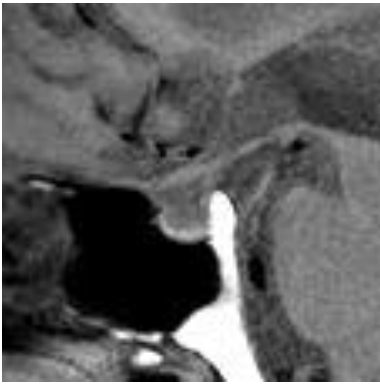
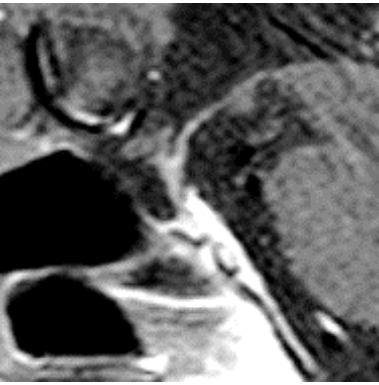
	Case 2	Case 3	Case 4	Case 5
MRI (T1-weighed)				
Diagnosis of autoimmune pancreatitis	Definitive	Definitive	Definitive	Definitive
Age (years) of the onset of IgG4-RD	76	70	81	65
Age (years) of the assessment of pituitary function and MRI	83	76	82	66
IgG4 concentration (mg/dL) at the onset IgG4-RD	379	1206	206	361
IgG4 concentration (mg/dL) at the assessment of pituitary function and MRI	210	400	206	940

Table 1. Clinical characteristics of the patients with autoimmune pancreatitis

Sex (male/female)	5/22
Diagnosis of autoimmune pancreatitis (Definite/Probable/Possible)	22/4/1
Age of onset of IgG4-RD	63.4 ± 12.1 (years)
Age of onset of autoimmune pancreatitis	64.5 ± 11.8 (years)
Age at assessment of pituitary function and MRI	68.6 ± 10.8 (years)
Time of assessment of pituitary function and MRI from the onset of IgG4-RD	3 [1, 7] (years)
Serum IgG4 levels at the onset of IgG4-RD	377 [227, 542] (mg/dL)
Serum IgG4 levels at the time of assessment of pituitary function and MRI	210 [103, 413] (mg/dL)
Other organ involvements of IgG4-RD	13, 48.1 (cases, %)
Total number	27
IgG4-RD; IgG4-related diseases, MRI; magnetic resonance imaging	

Table 2. The results of the basal hormone levels in case 1–5 and provocative test in case 1

		Case 1	Case 2	Case 3	Case 4	Case 5	normal range
Age		78	83	76	82	66	
Sex		M	M	M	M	M	
GH	(ng/mL)	0.3	1.7				
Peak GH	(ng/mL)	5.7					
ACTH	(pg/mL)	3.9	46.1	19.8	40.2	48.6	7.7 – 63.1
Peak ACTH	(pg/mL)	7.5					
Cortisol	(µg/dL)	1.0	13.3	6.5	36.2	13.5	
Peak Cortisol	(µg/dL)	1.1					
TSH	(µIU/mL)	0.8	2.6	3.1	1.0	2.8	0.4 – 5.0
Peak TSH	(µIU/mL)	2.9					
PRL	(ng/mL)	22.8	9.3	5.0	11.2	4.7	3.6 – 12.8
Peak PRL	(ng/mL)	39.5					
LH	(µIU/mL)	0.7	2.3	5.7	25	4.2	0.8 – 5.7
Peak LH	(µIU/mL)	2.9					
FSH	(µIU/mL)	2.1	8.5	26.7	50.2	5.6	0.7 – 11.5
Peak FSH	(µIU/mL)	4.3					
IGF-1	(ng/mL)	39.0	65.0	91.0	166.0	30.0	
SD score		-3.4	-1.5	-0.9	1.8	-4.1	
f-T4	(ng/dL)	0.9	1.1	1.1	1.0	1.0	0.7 – 1.5
Testosterone	(ng/mL)	< 0.1	5.8	7.1	5.3	4.8	2.9 – 9.5
prednisolone*	(mg/day)	5	-	2.5	-	-	
levothyroxine*	(µg/day)	25	-	-	-	-	

* dose at the assessment of the pituitary function and MRI

Table 3. multiple organ involvement in patients with pituitary abnormalities

	Case 1	Case 2	Case 3	Case 4	Case 5
Other organ involvement	Retroperitoneum, kidney, and lacrimal gland	(-)	Submandibular gland	Retroperitoneum, kidney, lacrimal gland, and submandibular gland	Lacrimal gland and aorta

Table 4. Reported cases of IgG4-related hypophysitis with autoimmune pancreatitis

Case No.	Author	Sex	Age at onset of IgG4-RD	Age at onset of Autoimmune pancreatitis	Age at onset of hypophysitis	IgG4 concentration at the onset of IgG4-RD (mg/dL)	Co-existing organ involvement except pancreas	Hypopituitarism	DI	Year	Reference
1	van der Vliet	F	63	63	66	485	Salivary gland, lung, and retroperitoneum	AF	-	2004	5
2	Taniguchi	M	66	66	75	N/D	Lung	AF	-	2006	21
3	Wong	M	73	73	77	720	Gallbladder	AF	-	2007	22
4	Ralli	M	67	67	67	elevated	(-)	AF	AF	2007	23
5	Tsuboi	M	62	62	62	292	Lung and retroperitoneum	AF	AF	2008	24
6	Bando	F	51	53	58	405	Salivary gland and lung	-	AF	2014	8
7	Bando	M	40	40	56	279	Retroperitoneum	-	AF	2014	8
8	Iseda	M	72	72	74	2100	Lung	AF	AF	2014	25
9	Joshi	M	67	67	4 months after	240	(-)	AF	AF	2015	26
10	Joshi	M	62	62	62	307	Retroperitoneum, kidney, and Lymph node	N/D	AF	2015	26
11	Koenigstein	M	81	81	83	3100	Choroid plexus, lymph node, aorta, lungs, and salivary gland	description only pituitary MRI findings		2016	27
12	Liu	F	26	N/D	44	1910	Lacrimal glands, thyroid gland, and submandibular gland		-	AF	2018

13	Kanie	M	66	68	78	802	Salivary gland, retroperitoneum, and kidney	AF	-	2018	present study
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IgG4-RD: IgG4-related disease, DI: diabetes insipidus, N/D: not described, and AF: affected

Supplementary Table 1. Diagnostic criteria of autoimmune pancreatitis [13] and IgG4-related hypophysitis [6].

Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011 (The Japan Pancreas Society, Research Committee for Intractable Pancreatic Disease by the Ministry of Labor, Health and Welfare of Japan)

【Diagnostic Criteria】

A. Diagnostic criterion

I. Enlargement of the pancreas :

- a. Diffuse enlargement
- b. Segmental/focal enlargement

II. ERP (endoscopic retrograde pancreatography) shows irregular narrowing of the main pancreatic duct

III. Serological findings

Elevated levels of serum IgG4 (≥ 135 mg/dl)

IV. Pathological findings: among i)~iv) listed below,

- a. three or more are observed
- b. two are observed

- i) Prominent infiltration and fibrosis of lymphocytes and plasmacytes
- ii) Ten or more diffuse IgG4-positive plasmacytes per high-power microscope field
- iii) Storiform fibrosis
- iv) Obliterative phlebitis

V. Other organ involvement (OOI): sclerosing cholangitis, sclerosing dacryoadenitis/ sialoadenitis, retroperitoneal fibrosis

a. Clinical lesions

Extra-pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis (Mikulicz disease), or retroperitoneal fibrosis can be diagnosed with clinical and image findings.

b. Pathological lesions

Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, or retroperitoneal fibrosis.

<Option> Effectiveness of steroid therapy

A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytological examination using an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis.

B. Diagnosis

I. Definite diagnosis

1 Diffuse type

I a + <III / IVb / V(a/b)>

2 Segmental/focal type

I b + II + two or more of <III / IV b / V (a/b)>

I b + II + <III / IV b / V (a/b)> + Option

3 Definite diagnosis by histopathological study

IV a

II. Probable diagnosis

Segmental/focal type:

I b + II + <III / IV b / V (a/b)>

III. Possible diagnosis*

Diffuse type:

I a + II + Option

Segmental/focal type:

I b + II + Option

When a patient with a focal/segmental image of AIP on CT/MRI without ERCP findings fulfill more than one of III, IVb and V(a/b) criteria, he/she can be diagnosed as possible AIP only after the negative workup for malignancy by EUS-FNA, and confirmed as probable one by an optional steroid response.

Possible diagnosis*: A case may be possibly type 2, although it is extremely rare in Japan.

”+” refers to “and”, and “/” refers to “or”.

Diagnostic criteria for IgG4-related hypophysitis

Criterion 1: Pituitary histopathology Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4positive cells per high-power field

Criterion 2: Pituitary MRI Sellar mass and/or thickened pituitary stalk

Criterion 3: Biopsy-proven involvement in other organs Association with IgG4-positive lesions in other organs

Criterion 4: Serology Increased serum IgG4 ($>140\text{mg/dl}$)

Criterion 5: Response to glucocorticoids Shrinkage of the pituitary mass and symptom improvement with steroids

Diagnosis of IgG4-related hypophysitis is established when any of the following is fulfilled:

Criterion 1

Criteria 2 and 3

Criteria 2, 4, and 5