Pituitary (2019) 22:54–61
https://doi.org/10.1007/s11102-018-00930-y

IgG4-related hypophysitis in patients with autoimmune pancreatitis

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Published online: 4 January 2019

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.

Keywords Hypophysitis · IgG4-related hypophysitis · Autoimmune pancreatitis · IgG4-related pancreatitis

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

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11102-018-00930-y) contains supplementary material, which is available to authorized users.

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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 (Fig. 1). The diagnosis of autoimmune pancreatitis was based on the clinical diagnostic criteria of autoimmune pancreatitis [12] (Supplementary Table 1). Briefly, 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), thyrotropin-releasing hormone (TRH) (200 μg), luteinizing hormone-releasing hormone (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 to 105 mg/dL. The criterion of

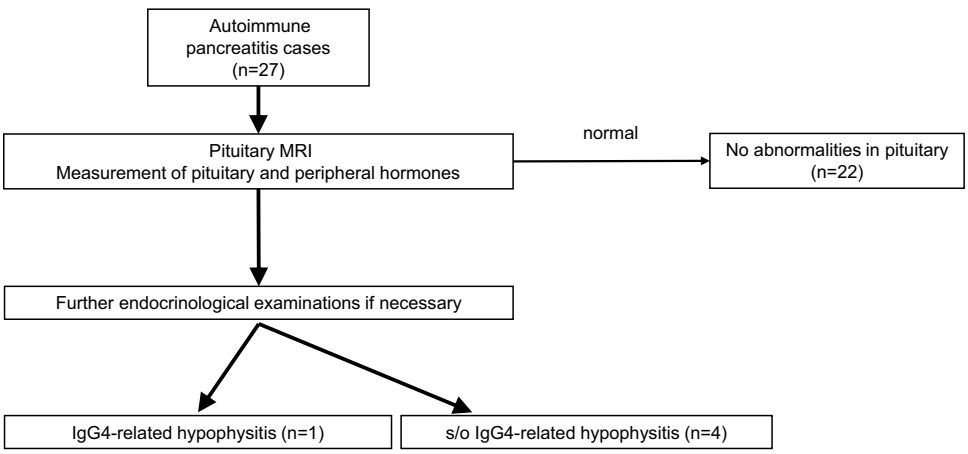


Fig. 1 Study design of the screening for IgG4-related hypophysitis

IgG4 levels in IgG4-RD were defined as more than 135 mg/dL [3, 12].

Statistical analysis

Data are expressed as means ± standard (SD) 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 (Fig. 2) and was diagnosed with hypopituitarism and the other 4 cases showed empty sella (Fig. 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

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

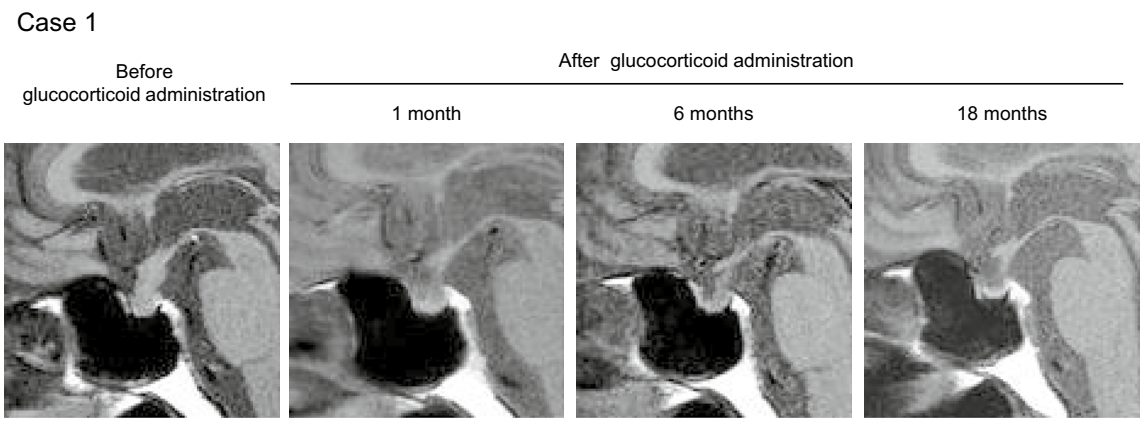


Fig. 2 Changes in the pituitary MRI findings of case 1 that showed a typical IgG4-related hypophysitis. Enlargement of the pituitary gland and thickened pituitary stalk shrank and became empty sella during the glucocorticoid treatment

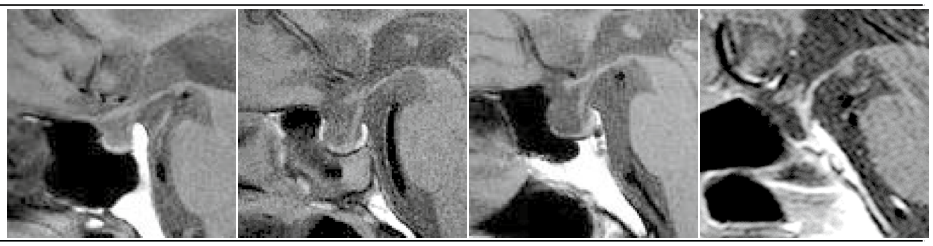
	Case 2	Case 3	Case 4	Case 5
MRI (T1-weighed)				
Diagnosis of autoimmune pancreatitis	Definitive	Definitive	Definitive	Definitive
Age (years) of the onset of IgG4-RD	76	70	81	65
Age (years) of the assessment of pituitary function and MRI	83	76	82	66
IgG4 concentration (mg/dL) at the onset IgG4-RD	379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

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

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 (Fig. 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 [thyroid stimulating hormone (TSH) 1.968 μIU/L (reference range 0.449–3.809 μIU/L) and thyroxine (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

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[a] (mg/day)	5	–	2.5	–	–	
Levothyroxine[a] (μg/day)	25	–	–	–	–	

[a]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

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 ± 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 pituitary underwent 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], 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 four cases with empty sella may be a result of hypophysitis but steroid therapy for autoimmune

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	References
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	[28]
13	Kanie	M	66	68	78	802	Salivary gland, retroperitoneum, and kidney	AF	–	2018	Present study

IgG4-RD IgG4-related disease, *DI* diabetes insipidus, *N/D* not described, and *AF* affected

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 adrenocorticotropic hormone (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.

Acknowledgements We thank K. Imura and C. Ogata for their excellent assistance.

Author contributions KK, HB, and GI performed analysis and interpretation of data and wrote the draft of the article. HS, AM, AS, TK, YS, and YK contributed to the preparation of the patient cohort. HF, HN, KY, RM, KS, and WO contributed to the assembly of data. YT contributed to the study supervision and critical revision of the article for important intellectual content.

Funding This work was supported by Japan Society for the Promotion of Science (JSPS) (KAKENHI, Grant numbers 23659477 and 26670459 [Y Takahashi], 23591354, 15K09431, and 18K08514 [G Iguchi], and 17K16165 [H Bando]), the Foundation for Growth Science (G Iguchi), the Japan Agency for Medical Research and Development (AMED) (17bm0804012h0001) (Y Takahashi), the Uehara Memorial Foundation (Y Takahashi), and the Naito Foundation (Y Takahashi).

Compliance with ethical standards

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

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