

NOTE

Putative IgG4-related pituitary disease with hypopituitarism and/or diabetes insipidus accompanied with elevated serum levels of IgG4

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Abstract. IgG4-positive plasma cell infiltration into multiple organs or tissues, such as the pancreas and salivary glands, associated with increased serum levels of IgG4 is a characteristic finding seen in IgG4-related disease. Affected organs may appear tumorous as a result of chronic inflammatory processes accompanied with progressive fibrosis. Recent cases of this disorder in which the pituitary gland was affected include cases of diffuse enlargement of the pituitary and/or its stalk associated with central diabetes insipidus and/or impaired anterior hormone production. Here we report two such cases, as well as two additional previously undiagnosed cases found in our database. In order to make a correct diagnosis of pituitary lesion involvement with IgG4-related disease, the clinical background and concomitant disorders should be carefully taken into consideration and the measurement of serum levels of IgG4 seems to be useful.

Key words: IgG4, Pituitary, Hypopituitarism, Diabetes insipidus

IGG4-RELATED disease, also called IgG4-positive multi-organ lymphoproliferative syndrome [1-3], is characterized by dense infiltration of IgG4-positive plasma cells (>50% of infiltrated IgG-positive cells) into multiple organs or tissues in association with increased serum levels of IgG4 (>135 mg/dL [1-3]). This disorder is frequently seen in older males who frequently have allergic disorders, and multiple organs or tissues can be affected, including the salivary glands (Mikulicz disease), pancreas (autoimmune pancreatitis), lungs (interstitial pneumonitis), retroperitoneal space (retroperitoneal fibrosis), kidneys (interstitial nephritis), and arachnoids (pachymeningitis); in addition, the disease can result in inflammatory pseudotumors at sites such as the orbits and lungs [2, 3]. Because of the chronic inflammatory process as-

sociated with progressive fibrosis in the lesions involved, the affected organs may appear tumorous.

Autoimmune pancreatitis (AIP) and Mikulicz disease (MD) are the major components of IgG4-related disease. AIP is one of the forms of chronic pancreatitis causing painless obstructive jaundice due to associated sclerosing pancreatitis. AIP is frequently seen in older males (mean age: 68.3 years old; ratio of males to females: 4 to 1), and impaired exocrine and/or endocrine pancreatic function is also frequently seen [3]. MD is a clinical condition characterized by bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands with mild dry eye and mouth. This disorder has long been confused as a subtype of Sjögren syndrome. Negative anti-SS-A and SS-B antibodies, high serum levels of IgG4, and an infiltration of IgG4-positive cells within the salivary gland now distinguish MD from Sjögren syndrome [3].

The pituitary gland can also be affected in IgG4-related disease (IgG4-related pituitary disease). There have been 8 published cases of pituitary lesions associated with this disease [4-11]. Central diabetes insipidus and/or disturbed anterior hormone production

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with tumor or tumor-like lesion formation in or near the pituitary, are commonly seen in these cases. A recent review of such cases described 22 clinical patients, most of them in Japan [12]. There was a clear preponderance of elderly males (~95% being male and the median age being 64 years old). Either anterior (~80%) or posterior pituitary function (~50%) was impaired with MRI findings of pituitary and/or stalk swelling. Most of the cases had either AIP and/or MD concomitantly. Serum levels of IgG4, when measured, were mostly elevated [12]. Here we report two such cases who developed panhypopituitarism associated with diabetes insipidus, and two additional cases found in our database.

Case 1

A 74-year-old female was referred to our department due to an acute development of pituitary failure. She had no allergic diathesis, but had been diabetic for 30 years and became anorectic after frequent episodes of hypoglycemia caused by insulin therapy. She was diagnosed with adrenal insufficiency based on her low serum levels of ACTH (13.4 pg/mL) and cortisol (4.6 µg/dL), and treated with 10 mg/day of hydrocortisone. Her clinical conditions improved, including her loss of appetite, but she noticed polydipsia and polyuria upon treatment. An anterior pituitary function test performed after admission showed a partial impairment of ACTH, LH, FSH (Fig. 1A) and GH (peak GH after stimulation with 100 µg of GHRP-2; 4.429 ng/mL). Masked diabetes insipidus was also diagnosed clinically and biochemically, and desmopressin spray was initiated.

Pituitary MRI showed a diffuse swelling of the entire pituitary; the pituitary stalk was markedly enhanced with gadolinium (Fig. 1B and C). In blood testing, the levels of angiotensin-converting enzyme, AFP, CEA, and anti-neutrophil cytoplasmic antibodies were not remarkable, and anti-thyroid autoantibodies were negative. Systemic CT scan and tuberculin skin test did not suggest active tuberculosis. Gallium scintigraphy showed hot spots in the cervical and hilar lymph nodes, but accumulation in the pituitary gland was not apparent (results not shown). We biopsied the cervical lymph node, which showed an infiltration of plasma cells, including IgG4-positive cells (~10% of IgG-positive cells) (Fig. 1F to I). Serum levels of IgG4 were also elevated (Fig. 1J), suggesting IgG4-

related disease involving the pituitary gland. There was a dramatic reduction of the swelling of the pituitary and its stalk after 2 weeks of treatment with 30 mg/day of prednisolone (Fig. 1D and E). A reduction of the serum levels of IgG4 and a slight increase of LH, FSH, and IGF-1 (Fig. 1J) were also observed during the tapering of prednisolone (prednisolone was reduced 5 mg/day every two weeks) down to a maintenance dose of 10 mg/day without apparent relapse for longer than four months.

Case 2

A 68-year-old male without any previous allergic disorders was admitted to our university hospital for treatment of diabetes insipidus. The pituitary MRI revealed a loss of the high signal in the pituitary posterior lobe in association with a pituitary mass-like lesion extending to the stalk (Fig. 2A and B). His anterior pituitary function was spared (Fig. 2G). Blood tests for angiotensin-converting enzyme, AFP, and CEA were negative, and a systemic CT scan and tuberculin skin test did not suggest active tuberculosis. This mass lesion was suspected to be lymphocytic infundibuloneurohypophysitis. The patient declined tumor biopsy or therapeutic diagnosis using glucocorticoids and he was discharged with replacement treatment of desmopressin. Three years after admission, he developed right-sided leg edema caused by retroperitoneal fibrosis, a diagnosis supported by the pathological findings of lymphocytic infiltration and fibrosis seen in the retroperitoneal mass around the right iliac artery. Hydrocortisone and thyroxine therapy were initiated 5 years after the first presentation as a result of the gradual loss of anterior pituitary function.

Seven years after the first admission, the patient was admitted again with a complaint of persistent headache that seemed to be caused by the enlarged pituitary lesion (Fig. 2C and D). Repeated blood testing including an assay for anti-thyroid autoantibodies did not suggest any causative disorders that might be causative of pituitary failure (Fig. 2G) except high serum levels of IgG4 (Fig. 2H). We were also able to measure the serum level of IgG4 one year prior to the last admission by using the stock sera; the serum IgG4 was 151 mg/dL at this time point. There was gallium accumulation in the cervical, supraclavicular, and bilateral hilar lymph nodes, and a retroperitoneal mass around the right iliac artery, but accumulation in the

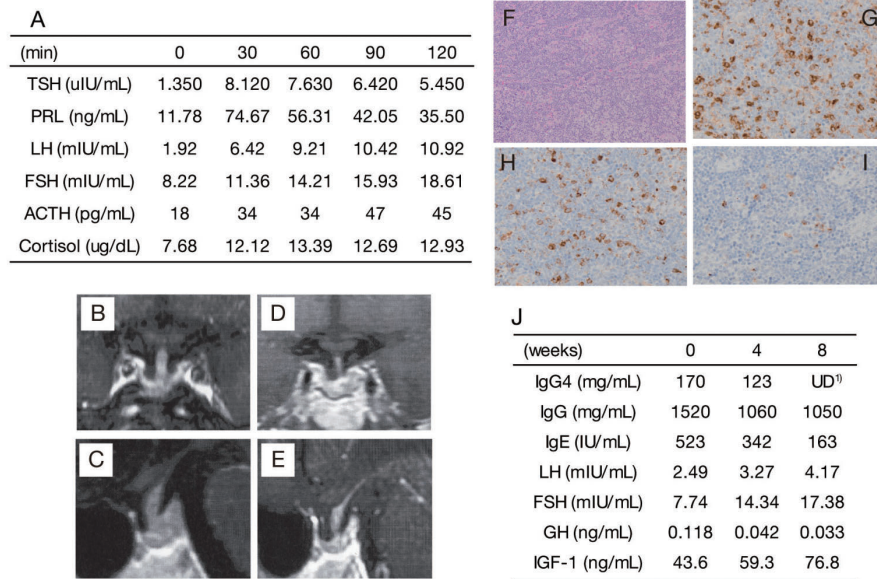


Fig. 1 Hormonal data and MRI findings of Case 1.

(A) Pituitary hormone responses to the secretagogues (500 μ g of TRH, 100 μ g of LHRH, and 100 μ g of CRH) are shown. Blood samples were obtained before and after stimulation as indicated.

(B to E) Pituitary images of Case 1 before (B and C) and after (D and E) prednisolone treatment. Note that the enlarged pituitary gland and stalk, which are well enhanced with the gadolinium contrast media and remarkably reduced after two weeks of treatment with prednisolone.

(F to I) Histological findings of a cervical lymph node from Case 1. There is no apparent infiltration of histiocytes or neoplastic cells, and no granuloma formation is seen (F). Infiltration of plasma cells (G), IgG-positive cells (H), and IgG4-positive cells (I). Hematoxylin and eosin (F: x200). Immunostaining with anti-CD 38 antibody (G), anti-IgG antibody (H), anti-IgG4 antibody (I) (G to I: x400).

(J) Immunological and hormonal parameters before and after prednisolone therapy. ¹⁾UD; Undetermined.

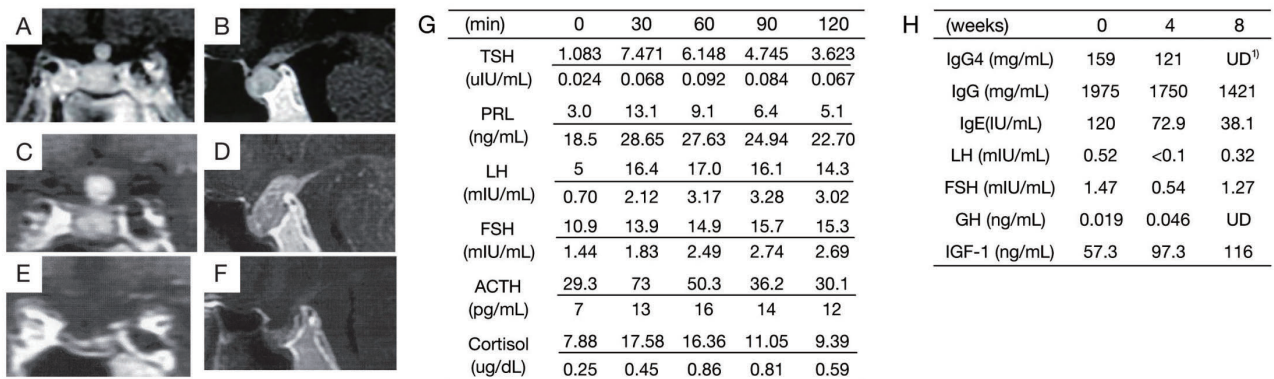


Fig. 2 Hormonal data and MRI findings of Case 2.

(A to F) Pituitary images of Case 2 obtained at the initial presentation at 68 years of age (A and B), and before (C and D) and after (E and F) prednisolone treatment. Note the gradual progression of the enlargement of the pituitary gland and its stalk, which are well enhanced with the gadolinium contrast media and remarkably reduced after two weeks of treatment with prednisolone.

(G) The pituitary hormone responses to the secretagogues (500 μ g of TRH, 100 μ g of LHRH, and 100 μ g of CRH) are shown. Blood samples were obtained before and after stimulation as indicated. Data above the lines were obtained at the initial presentation and those below were obtained seven years after the initial presentation.

(H) Immunological and hormonal parameters before and after prednisolone therapy. The reduction of LH and FSH after prednisolone therapy was most likely due to initiation of sex steroid replacement. ¹⁾UD; Undetermined.

pituitary gland was not apparent. The pituitary lesion was clinically suspected to be IgG4-related pituitary disease. Two weeks after treatment with 30 mg/day of prednisolone, there was a dramatic reduction in the swelling of the pituitary and its stalk (Fig. 2E and F). A reduction of the serum levels of IgG4 and slight increase of IGF-1 (Fig. 2H) were also observed during the tapering of prednisolone (prednisolone was reduced 5 mg/day every two weeks) down to a maintenance dose of 10 mg/day without apparent relapse for longer than three months.

Retrospective survey of our database

Because of the similarity of the MRI findings of the pituitary gland and its stalk between Case 1 and 2, we reviewed the MRI findings of the previous cases admitted to our department and determined the serum levels of IgG4 by using the stock sera of the cases with compatible MRI findings.

Methods

We reviewed the charts of 95 patients who were admitted to our department from January of 2000 to June of 2008. These patients were selected from our database by using keywords such as pituitary, panhypopituitarism, diabetes insipidus, ACTH, adenohypophysitis and infundibuloneurohypophysitis. We were able to find 4 cases other than the above-described Case 1 and 2 with pituitary MRI findings of a diffuse swelling of the entire pituitary and/or its stalk enhanced with gadolinium. In patients receiving corticosteroid replacement, the serum levels of IgG4 (SRL Inc., Tokyo, Japan) were determined by using the stock sera obtained before the start of treatment. Serum levels of IgG4 >135 mg/dL were considered significantly high [1-3].

Results

Four of the identified cases (Cases 3-6 in Table 1) had been clinically diagnosed with either lymphocytic adenohypophysitis or infundibuloneurohypophysitis, and showed clinical and laboratory findings of insufficient production of either anterior or posterior pituitary hormone(s). Serum levels of IgG4 were elevated in two of four cases (Cases 3 and 4). The pituitary MRI findings of these cases are shown in Figure 3. When Cases 1 and 2 were included, there was no male preponderance (2 males and 2 females), but the age of onset remained fairly late (average 68.5 years

old). Central diabetes insipidus was seen in three and impaired anterior pituitary function in two cases at the initial presentation. Other organ manifestations seen were interstitial pneumonitis and pachymeningitis in Case 3. No other organ manifestation was been detected in Case 4 *per se*. We were not able to find any differences in clinical presentation or MRI findings between patients with or without elevated serum levels of IgG4.

Discussion

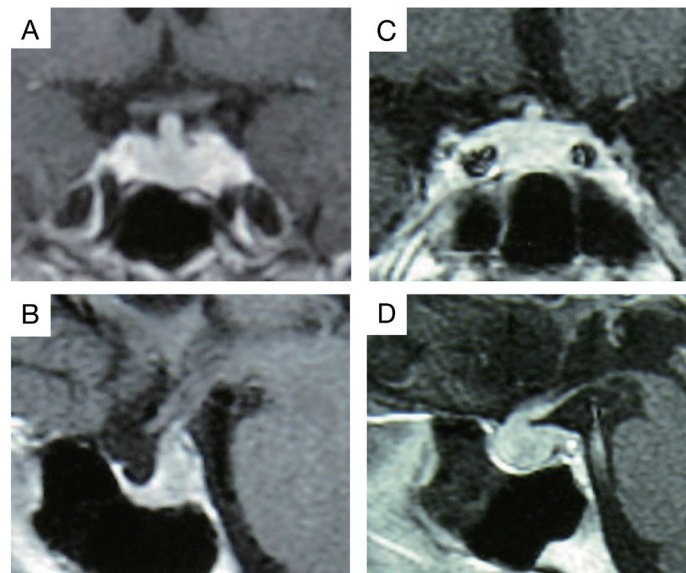
Our cases reported here were suspected of having IgG4-related pituitary disease based on characteristic MRI findings along with high serum levels of IgG4. Since we did not examine the pituitary tissue, the major concern was the differential diagnosis. It has been shown that an elevated serum level of IgG4 (>135 mg/dL) is a sensitive marker for a diagnosis of AIP [13, 14], and, therefore, this is included as one of the diagnostic criteria for IgG4-related disease [1-3]. However, it should be stressed that in some patients with pancreatic cancer, an important condition in the differential diagnosis of AIP, high serum levels of IgG4 (>140 mg/dL) were indeed found and a higher cut-off (>280 mg/dL) has been suggested to improve specificity [15]. In addition, serum levels of IgG4 can be elevated in Wegener granulomatosis, multicentric Castleman's disease, and idiopathic plasmacytic lymphadenopathy [1]. Thus, high serum levels of IgG4 alone can not be used to make a diagnosis of IgG4-related disease. In our index cases, such disorders were excluded by blood tests, including assays for negative anti-neutrophil cytoplasmic antibodies and systemic CT, and by the biopsy findings from the cervical lymph nodes and retroperitoneal masses.

Swelling of the pituitary and its stalk is seen in conditions such as lymphocytic hypophysitis, sarcoidosis, tuberculosis and Wegener's granulomatosis. Among these, lymphocytic hypophysitis (LYH) is an important disorder to be differentiated, since LYH is occasionally diagnosed solely based on the MRI findings [16, 17]. LYH is characterized by lymphocytic infiltration leading to the destruction of the pituitary gland in association with an impaired pituitary function, either in the anterior pituitary and/or posterior lobe [16, 18]. LYH is common in young females, particularly in association with late pregnancy or the postpartum period (~60% of the cases with LYH), and peaks in inci-

Table 1 Clinical presentations and serum levels of IgG4 of the cases with pituitary enlargement.

Case #	Age/Sex	Presentation ¹⁾	IgG	IgG4	Other organ involvement
1	74/F	ACTH,LH, FSH, GH ADH	1520	170	cervical and hilar lymph nodes
2	68/M	ADH	1975	159	cervical and hilar lymph node, and retroperitoneal fibrosis
3	72/M	ACTH,TSH	1550	167	interstitial pneumonitis, pachymeningitis
4	60/F	ADH	1504	201	none
5	80/M	ACTH	1736	92	none
6	24/M	ADH	1063	16	none

¹⁾Indicates defective pituitary hormone(s) at the initial presentation. The reference ranges are 4.8-105 (mg/dL) for IgG4, and 870-1700 (mg/dL) for total IgG. The values exceeding the reference ranges are shown in bold.

**Fig. 3** Pituitary MRI findings of Cases 3 and 4.

Pituitary MRIs with gadolinium contrast media in Cases 3 and 4.

In Case 3 the posterior lobe of the pituitary and the stalk are swollen while the anterior lobe is partially atrophic (A and B). In Case 4 the posterior lobe appears tumorous and compresses the anterior lobe (C and D).

dence in the 4th decade of life [16], but cases of male and elderly individuals have also been reported [16, 18]. It has been shown that some cases with lymphocytic adenohypophysitis can be successfully treated with a small dose of prednisolone, such as 15 to 40 mg per day for 2 weeks to 3 months, but other cases have required high dose methylprednisolone pulse therapy [17]. Based on the clinical picture, our cases may have been diagnosed as late-onset LYH. Indeed, two of the cases with a putative diagnosis of IgG4-related pituitary disease identified in our database (Cases 3 and 4) were originally clinically diagnosed as cases of

LYH.

How can LYH and the pituitary lesions associated with IgG4-related disease be differentiated? A pituitary biopsy with IgG4 staining would be the most straightforward method. However, in the absence of such an invasive examination of the pituitary tissue, the patient background and concomitant disorders should be carefully taken into consideration (Table 2). Concomitant autoimmune disorders tend to favor a diagnosis of LYH and allergic disorders, and the organ manifestations seen in IgG4-related disease, such as AIP, strongly suggest IgG4-related pituitary disease.

Table 2 Clinical features associated with lymphocytic hypophysitis and IgG4-related pituitary disease.

	IgG4-Related pituitary disease	Lymphocytic hypophysitis
Age	seventh decade of life	fourth decade of life
Sex	male dominant	female dominant
Pituitary MRI	diffuse swelling	diffuse swelling
Hormonal impairment	anterior and/or posterior	anterior and/or posterior
Associated disorders	allergic disorders	autoimmune disorders
	autoimmune pancreatitis	autoimmune thyroiditis
	Mikulicz disease	type 1 diabetes
	retroperitoneal fibrosis	autoimmune adrenalitis
Serum markers	high IgG4 ¹⁾	anti-pituitary antibodies

Clinical features of these two disorders are summarized based on the literature [1, 12, 18].

¹⁾ Serum levels of IgG and IgE may also be elevated [1].

Anti-pituitary antibodies may favor a diagnosis of LYH [16], and high serum levels of IgG4 may favor IgG4-related pituitary disease; however, these findings are still non-specific. In this study, therefore, Cases 2 and 3 were considered reasonably likely to be cases of IgG4-related pituitary disease with concomitant disorders and elevated serum levels of IgG4. In Case 1, this diagnosis was suspected based on IgG4-positive cell infiltration in the cervical lymph nodes and by excluding other disorders. The therapeutic response to corticosteroids also supported the diagnosis in Cases 1 and 2. The problematic case would be one with a pituitary lesion with MRI findings suggesting LYH and IgG4-related pituitary disease, but without any concomitant autoimmune or allergic disorders, or any other organ involvement associated with IgG4-related disease, such as in Case 4 in our study. A similar case with central diabetes insipidus, which was assumed to have been caused by a primary tumor or lymphocytic infundibuloneurohypophysitis, was recently reported [11]. After two years of stable clinical course, this case showed rapid development of panhypopituitarism associated with an enlargement of the pituitary, which turned out to be IgG4-related pituitary disease [11]. Therefore, measurement of the serum anti-pituitary antibodies and/or IgG4 would be useful, but still non-specific, for identifying the putative cause of pituitary failure in such cases, and could provide clues to the

most appropriate management of the patient. When neither marker is positive, careful observation would be important, including repeated measurement of these markers. When the serum IgG4 levels are elevated, a systemic survey should be considered to detect other organs involved with IgG4-related disease by using gallium scintigraphy and/or FDG-PET [19]. In the cases we reported herein, we did not observe gallium accumulation in the pituitary. We are not certain if this was because gallium scintigraphy is less sensitive than FDG-PET for detecting IgG4-related disease, or whether it was related to the relative size of the lesion and/or the relative degree of inflammation.

In conclusion, we reported four putative cases of IgG4-related pituitary disease. These cases were suspected based on the typical MRI findings and elevated serum levels of IgG4. Our findings suggest that an overall consideration of the clinical picture and measurement of the serum levels of IgG4 may assist in the diagnosis of this disorder.

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