Endocrinology, Diabetes & Metabolism CASE REPORTS

N Nishi and others | IgG4-related hypophysitis

ID: 21-0029; July 2021
DOI: 10.1530/EDM-21-0029

Deterioration of pituitary function without relapse after steroid therapy for IgG4-related hypophysitis

Nobuyuki Nishi[1], Ken Takeshima[1], Shuhei Morita[1], Hiroshi Iwakura[1], Masahiro Nishi[1,2] and **Takaaki Matsuoka[1]**

[1]First Department of Internal Medicine and [2]Division of Clinical Nutrition and Metabolism, Wakayama Medical University, Kimiidera, Wakayama City, Wakayama, Japan

Correspondence should be addressed to K Takeshima
Email
kt10948@wakayama-med.ac.jp

Summary

IgG4-related hypophysitis is an autoimmune hypophysitis associated with IgG4-related disease. Swelling of the pituitary gland is responsive to steroid therapy, but the prognosis of pituitary function after the treatment remains unclear. The present case implies that transiently improved pituitary function can re-worsen during long-term follow-up in IgG4-related hypophysitis. A 71-year-old male patient with IgG4-related hypophysitis visited a nearby hospital with malaise, anorexia, and polyuria. Pituitary dysfunction was suspected, so he was referred to our hospital for further examination. Imaging studies and laboratory data showed swelling of the pituitary gland and panhypopituitarism, which dramatically improved following steroid therapy. There was no evidence of relapsing IgG4-related disease during prednisolone tapering. Pituitary function was examined after 4 years under treatment with low-dose prednisolone; surprisingly, anterior pituitary function had worsened again. Our case suggests a need for continuous monitoring of pituitary function after steroid therapy for IgG4-related hypophysitis. This report illustrates the natural course of pituitary function in IgG4-related hypophysitis and may be informative when considering the introduction of steroid therapy.

Learning points:

- Steroid therapy is an effective first-line therapy for pituitary dysfunction and pituitary swelling in IgG4-related hypophysitis.
- Pituitary function can worsen again during follow-up, despite transient improvement after steroid therapy in IgG4-related hypophysitis.
- Continuous monitoring of pituitary function is necessary for IgG4-related hypophysitis, regardless of disease activity.

Background

IgG4-related disease (IgG4-RD) is a multi-organ disorder characterized by high serum IgG4 levels and massive lesions with severe fibrosis and infiltration of IgG4-positive plasma cells. The typically affected organs include the pancreas, lacrimal glands, salivary gland, thyroid, lungs, kidneys, and the retroperitoneum; the pituitary gland can also be affected (1, 2).

IgG4-related hypophysitis is commonly observed in elderly men and presents as a thickened pituitary stalk and pituitary mass. Histopathological features of the pituitary lesion are dense infiltration of IgG4-positive plasma cells and fibrosis (3). Symptoms associated with swelling of the pituitary gland are headaches, visual disturbances, and nausea. Pituitary dysfunction can

ID: 21-0029; July 2021
DOI: 10.1530/EDM-21-0029

cause nausea, malaise, weight loss, decreased libido, polydipsia, and polyuria (1).

Steroid therapy is the first choice of treatment for IgG4-related hypophysitis (4). In one study, more than 90% of patients were reported to have reduced swelling of pituitary lesions after steroid therapy (5). Elsewhere, more than 60% of patients have no improvement of pituitary function after steroid therapy (6, 7).

IgG4-related hypophysitis has been shown to relapse during steroid tapering (3), but in patients without relapse, the prognosis of pituitary function after steroid therapy has not been clarified.

Case presentation

A 71-year-old man visited a nearby hospital with malaise and anorexia. He was a non-drinker and had no notable family history but had a medical history of lacunar infarction. He had smoked 20 cigarettes per day for 40 years. His malaise began 8 months previously and gradually worsened. He also felt a loss of appetite, and on admission, his dietary intake was half of what it had been recently. He also had polydipsia and polyuria, needing to urinate more than 10 times per day. Pituitary dysfunction was suspected, so he was referred to our hospital for further examination and treatment. He was alert and oriented on admission, body temperature was 36°C, blood pressure was 109/80 mmHg, and heart rate was 75 b.p.m with a regular rhythm. On examination, he presented swelling of both submandibular glands. Respiratory and heart sounds were normal. His abdomen was soft and flat, without tenderness.

Investigation

Laboratory tests revealed hyponatremia of 127.0 mmol/L and slightly low blood glucose levels of 80 mg/dL. White blood cell counts were 5.90 × 10^9/L, and eosinophil counts were 0.377 × 10^9/L. Daily urine volume was approximately 2.5 L with relatively low urine osmolality of 289 mmol/kg. MRI showed swelling of the pituitary gland and stalk (Fig. 1A). The pituitary lesion was contrast-enhanced, suggesting the presence of hypophysitis. Lack of T1 signal hyperintensity in the posterior pituitary gland suggested diabetes insipidus.

Pituitary provocative tests were performed to assess pituitary functions (Table 1 and Fig. 2, X: open circle with dotted line). Basal adrenocorticotrophic hormone (ACTH) and cortisol levels were 1.4 pmol/L (range 1.6–13.9 pmol/L) and 309.0 nmol/L (range 195.9–540.8 nmol/L), respectively. ACTH secretion was delayed, and cortisol response was relatively low after corticotrophin-releasing hormone (CRH) stimulation. Basal free thyroxine (fT4) and free triiodothyronine (fT3) levels were relatively low, corresponding with the decrease in thyroid-stimulating hormone (TSH) level: TSH 0.068 mU/L (range 0.5–5.0 mU/L), fT4 12.4 pmol/L (range 11.6–21.9 pmol/L), and fT3 3.35 pmol/L (range 3.53–6.14 pmol/L). TSH and fT3 secretion were low after thyrotropin-releasing hormone stimulation. Basal and peak prolactin (PRL) levels were not decreased. Basal serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were low; they also showed low response to luteinizing hormone-releasing hormone stimulation. Insulin-like growth factor-1 was low, 57 μg/L (range 61–202 μg/L). Growth hormone (GH) secretion after growth hormone-releasing peptide-2 stimulation was extremely reduced, so we diagnosed severe GH deficiency. Anterior pituitary functions were suggested to be exacerbated due to hypophysitis. Regarding posterior pituitary function, secretion of arginine vasopressin (AVP) was insufficient, corresponding with an increase in serum sodium levels after hypertonic saline infusion. After administration of vasopressin, urinary osmolality increased from 289 to 557 mmol/kg. We, therefore, diagnosed partial central diabetes insipidus.

To investigate the cause of hypophysitis, we performed additional laboratory tests and imaging studies. Anti-neutrophil cytoplasmic antibodies and interferon-gamma release assay for *Mycobacterium tuberculosis* were negative. Chest X-ray showed no masses or hilar calcification. On

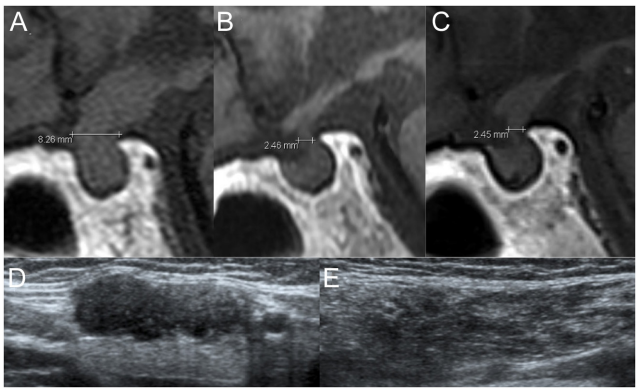

Figure 1
Imaging studies. MRI shows an improvement of the swelling of the pituitary gland after steroid therapy; (A) before treatment, (B) 1 year after steroid therapy, (C) 4 years after steroid therapy. Diameters of the pituitary stalk are (A) 8.26 mm, (B) 2.46 mm, and (C) 2.45 mm. Ultrasonography also shows improvement of the swelling and echogenicity in the submandibular gland; (D) before treatment, (E) 4 years after steroid therapy.

Table 1 Basal endocrine laboratory tests during steroid therapy.

	SI unit	Reference range	Before treatment	1 year after treatment	4 years after treatment
ACTH	pmol/L	(1.6–13.9)	1.4	0.8	1.7
Cortisol	nmol/L	(195.9–540.8)	309.0	16.6	206.9
LH	IU/L	(1.7–11.2)	<0.2	6.6	0.9
FSH	IU/L	(2.1–18.6)	1.4	14.7	3.9
TSH	mU/L	(0.50–5.00)	0.07	0.03	0.53
fT3	pmol/L	(3.53–6.14)	3.35	4.18	3.10
fT4	pmol/L	(11.6–21.9)	12.4	23.2	16.0
PRL	μg/L	(3.6–16.3)	15.0	9.9	14.0
GH	μg/L	(0–2.1)	<0.1	0.2	0.2
IGF-1	μg/L	(61–202)	57	111	73

ACTH, adrenocorticotropic hormone; fT3, free triiodothyronine; fT4, free thyroxine; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; PRL, prolactin.

the other hand, serum IgG4 levels were high with 264 g/L (>135 g/L), so we suspected IgG4-related hypophysitis.

We then examined for the systemic lesions associated with IgG4-RD. Ultrasonography of the neck showed bilateral swelling of the submandibular glands with heterogeneous low echogenicity (Fig. 1D). CT of the chest and abdomen showed no other organ lesions associated with IgG4-RD.

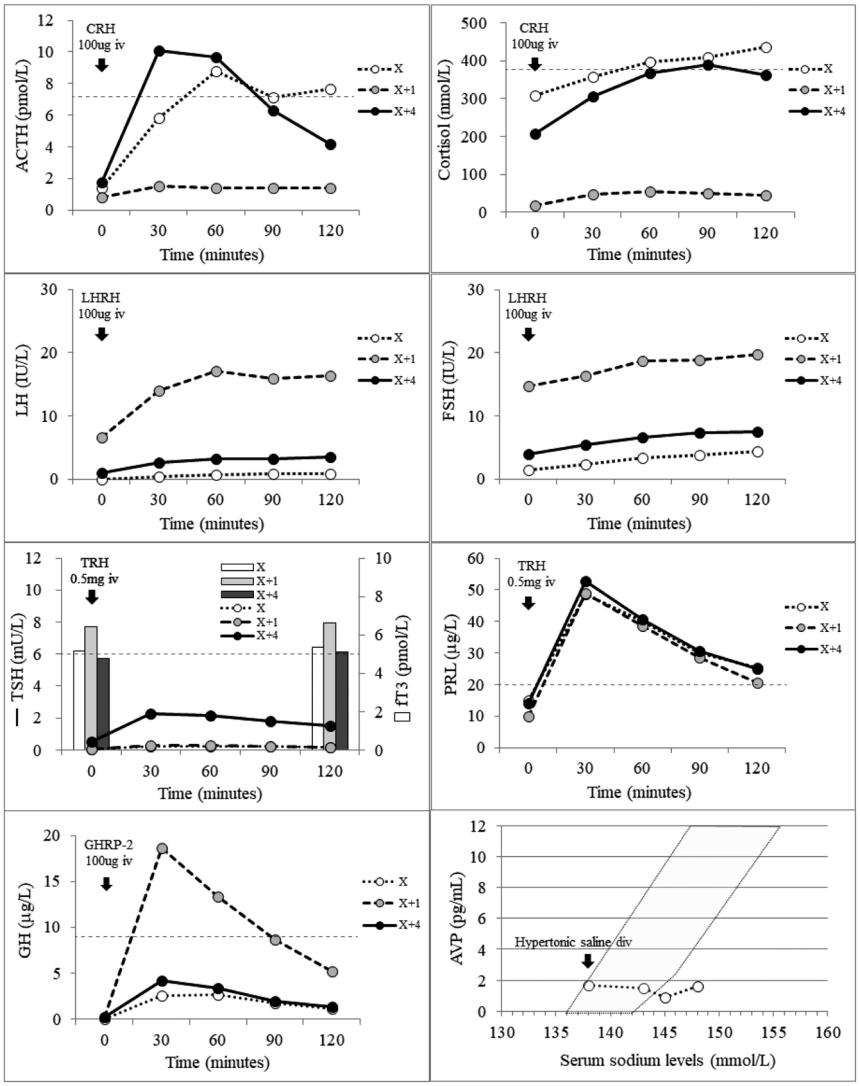

Figure 2
Pituitary function tests. CRH stimulation tests showed delayed secretion of ACTH and cortisol levels on the first admission, which would not improve after 4 years. LHRH stimulation test showed a low response of LH and FSH secretions, which partially improved after 1 year, but worsened again after 4 years. TRH stimulation test showed decreased secretion of TSH during steroid therapy, despite a slight increase in peak TSH levels after 4 years. PRL secretion after TRH stimulation was normal during steroid therapy. GHRP-2 test showed severely deteriorated GH secretion on the first admission, which improved dramatically after 1 year but worsened again after 4 years. Reference range of serum ACTH, cortisol, TSH, PRL, and GH levels is shown as dotted lines. Normal peak response of LH and FSH is defined as five-fold and two-fold increase after LHRH stimulation, respectively. Normal response of fT3 is defined as 1.3-fold after TRH stimulation. Reference range of serum AVP levels after the hypertonic saline infusion is shown as an area enclosed by dotted lines. X: before treatment (open circle with dotted line), X+1: 1 year after steroid therapy (closed gray circle with dashed line), X+4: 4 years after steroid therapy (closed black circle with solid line)ACTH, adrenocorticotrophic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; GH, growth hormone; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotropin-releasing hormone; fT3, triiodothyronine; div, i.v. drip.

ID: 21-0029; July 2021
DOI: 10.1530/EDM-21-0029

Salivary gland biopsy was performed for pathological diagnosis of IgG4-RD. Pathological findings of the submandibular gland showed infiltration of lymphocytes and plasma cells with severe fibrosis. Immunostaining revealed infiltration of IgG4-positive plasma cells: IgG4-positive plasma cells, 100/HPF; IgG4/IgG-positive plasma cell ratio, 50%. The patient was diagnosed with IgG4-related hypophysitis based on the diagnostic criteria (4).

Treatment

The patient was treated with hydrocortisone 15 mg/day and levothyroxine (LT4) 25 μg/day for hypoadrenocorticism and hypothyroidism at the nearby hospital 3 months before admission. Anorexia and malaise improved dramatically after the treatment. He felt unusually frequent urination after hydrocortisone therapy, which suggested the presence of masked diabetes insipidus. Hyponatremia improved after administration of hydrocortisone and levothyroxine. He was then referred to our hospital where he also received treatment with desmopressin 60 μg/day for central diabetes insipidus. Two weeks after admission, he was pathologically diagnosed with IgG4-RD and began treatment with prednisolone 35 mg/day. The swelling of bilateral submandibular glands improved dramatically within a few weeks. Prednisolone doses were gradually reduced to 6 mg/day over 1 year. Four years after starting steroid therapy, he was treated with prednisolone 2 mg/day for IgG4-RD and hydrocortisone 5 mg/day for secondary adrenal insufficiency. LT4 doses were adjusted to 50 μg/day to maintain thyroid function. Laboratory tests and imaging studies showed no evidence of relapsing IgG4-RD during the course of treatment.

Outcome and follow-up

MR imaging was performed 1 year after beginning steroid therapy. There was a marked improvement in the swelling of the pituitary gland and pituitary stalk (Fig. 1B). Pituitary function tests also showed significant improvement of the secretion of LH, FSH, and GH (Fig. 2, X+1: gray circle with dashed line). Assessment of the hypothalamic-pituitary-adrenal (HPA) axis was difficult because the patient had been administered 6 mg/day of prednisolone at that time. This steroid therapy may have suppressed pituitary inflammation, leading to the improvement of anterior pituitary function, but not posterior pituitary function. Serum IgG4 levels or pituitary swelling did not worsen, despite dose tapering of prednisolone to 2 mg/day.

Four years after starting steroid therapy, the patient was hospitalized to examine the cause of anemia. There were no obvious symptoms of pituitary dysfunction. At that time, he was treated with prednisolone 2 mg/day, hydrocortisone 5 mg/day, LT4 50 μg/day, and desmopressin 60 μg/day for hypopituitarism. There had been no increase in his requirements of LT4, hydrocortisone, or vasopressin during the course of treatments. Surprisingly, pituitary function tests showed re-exacerbation, especially for LH, FSH, and GH secretion (Fig. 2, X+4: black circle with solid line). Serum testosterone levels decreased from 8.1 to ≤ 0.15 nmol/L.

We suspected exacerbation of IgG4-related hypophysitis, but laboratory data and imaging studies showed no evidence of reoccurrence (Fig. 1 and Table 2). Serum IgG4 levels remained within the normal range (106 g/L), there was no worsening of pituitary swelling according to MR imaging. In addition, ultrasonography of the neck showed continued shrinkage of the submandibular glands. Whole-body CT scan confirmed no involvement of other new organs. We, therefore, speculated that the pituitary function decreased without relapse during the natural course of treatment, despite transient improvement after steroid therapy. Testosterone replacement therapy for hypogonadotropic hypogonadism was considered for the prevention of osteoporosis and sarcopenia, but the patient opted against the treatment. Endoscopic screening was performed to elucidate the cause of iron deficiency anemia,

Table 2 Laboratory data associated with the activity of IgG4-related hypophysitis.

	SI unit	Reference range	Before treatment	1 year after treatment	4 years after treatment
Immunoglobulin G4	g/L	(5–117)	264	87	106
Immunoglobulin G	g/L	(861–1747)	1597	894	972
Eosinophils	$\times 10^9$/L	(0.100–0.300)	0.380	ND	0.169
Soluble interleukin 2 receptor	U/mL	(122–496)	608	ND	673
Complement 3	g/L	(73–138)	122	ND	117
Complement 4	g/L	(11–31)	31	ND	31
Complement 50	g/L	(30–46)	41	ND	41

ND, not determined.

which revealed the presence of gastric cancer. The patient underwent chemotherapy without surgery because there were liver metastases. Considering the risk of umor growth, we did not start GH supplementation.

Discussion

Our case is characterized by the re-worsening of pituitary function without relapse after steroid therapy for IgG4-related hypophysitis. We believe that his clinical course may be informative when considering the introduction of steroid therapy.

IgG4-related hypophysitis is reported to be highly responsive to steroid therapy, but its effect is generally evaluated by the improvement of pituitary swelling (4). Meanwhile, the effectiveness of steroid therapy for the pituitary function is still debated and differs between reports. According to a literature review by Iseda *et al.*, anterior pituitary function after steroid therapy improved in 37.5% of patients with IgG4-related hypophysitis, although no patients had improvement of posterior pituitary function (7). Bando *et al.* showed no improvement of pituitary function after steroid therapy in patients with IgG4-related hypophysitis, although their study included only a small number of patients (6).

In our patient, anterior pituitary function, but not posterior pituitary function, improved after steroid therapy, as was shown in the report by Iseda *et al.* Significant improvement of anterior pituitary function was confirmed, especially in LH, FSH, and GH.

Lymphocytic hypophysitis often presents as adenohypophysitis, and ACTH is reportedly the most frequently damaged pituitary hormone, followed by LH/FSH, TSH, ADH, GH, and PRL (8). In contrast, IgG4-related hypophysitis frequently presents panhypophysitis and destroys pituitary hormones in the following order: ADH, LH/FSH, ACTH, TSH, GH, and PRL (5, 9). The differing patterns of impaired hormones could be attributed to the different locations of the inflammation. Our patient also presented panhypophysitis, so there was impairment of both anterior and posterior pituitary hormones.

The clinical course of autoimmune hypophysitis is divided into acute, subacute, and chronic phases (10). In the acute and subacute phases, pituitary edema due to the inflammation causes compressive symptoms, such as headaches and visual impairment. Cytokines produced at the sites of inflammation activate HPA axis, which leads to hypersecretion of cortisol. Transient recovery of pituitary function can be expected in the early phase when the pituitary edema improves by the reactive cortisol hypersecretion or steroid administration (8). In the chronic phase, on the other hand, pituitary fibrosis and atrophy cause secondary hypopituitarism. Variation in reported improvement rates in pituitary function may be attributed to the stage when steroid therapy is introduced, or to the duration after the therapy when the pituitary function is assessed.

In the currently reported case, we speculate that steroid therapy suppressed pituitary inflammation and edema, leading to transient improvement of pituitary function in the acute phase. Chronic progression of the fibrosis at the pituitary lesion could, however, result in secondary hypopituitarism.

Severe fibrosis, so-called storiform fibrosis, is one of the characteristic histopathological features of IgG4-RD and has also been confirmed in IgG4-related hypophysitis (6). This pathological feature may be associated with the reduction of pituitary function in IgG4-related hypophysitis during long-term follow-up. In the presently reported patient, we could not confirm pathological features of the pituitary lesion.

Indication of steroid therapy for IgG4-related hypophysitis requires careful consideration because of the risk of side effects and the possibility of reoccurrence during steroid tapering (1). Severe symptoms of compression by pituitary lesions are a good indication for therapy (11). Whether pituitary function will be preserved after treatment is also an important factor when initiating the therapy. Our patient's clinical course showed that the pituitary function can be damaged, despite transient improvement after steroid therapy, although more cases are needed for a conclusive result.

The presently reported case implies that pituitary function can exacerbate without relapse after steroid therapy for IgG4-related hypophysitis during long-term follow-up. Continuous monitoring of pituitary function is, therefore, needed, even without apparent signs of reoccurrence.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This study was partly supported by JSPS KAKENHI (Grant Number 20K17518).

Patient consent
Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement

N Nishi is an endocrinologist physician who followed the patient during hospitalization and wrote the first draft. K Takeshima is the corresponding author and responsible for organizing this article. M Nishi, S Morita, and H Iwakura are endocrinologist physicians who followed the patient. T Matsuoka is Director of the First Department of Internal Medicine and approved the final draft.

References

1 Shimatsu A, Oki Y, Fujisawa I & Sano T. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. *Endocrine Journal* 2009 **56** 1033–1041. (https://doi.org/10.1507/endocrj.K09E-277)

2 Takeshima K, Li Y, Kakudo K, Hirokawa M, Nishihara E, Shimatsu A, Takahashi Y & Akamizu T. Proposal of diagnostic criteria for IgG4-related thyroid disease. *Endocrine Journal* 2021 **68** 1–6. (https://doi.org/10.1507/endocrj.EJ20-0557)

3 Leporati P, Landek-Salgado MA, Lupi I, Chiovato L & Caturegli P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1971–1980. (https://doi.org/10.1210/jc.2010-2970)

4 Takagi H, Iwama S, Sugimura Y, Takahashi Y, Oki Y, Akamizu T & Arima H. Diagnosis and treatment of autoimmune and IgG4-related hypophysitis: clinical guidelines of the Japan Endocrine Society. *Endocrine Journal* 2020 **67** 373–378. (https://doi.org/10.1507/endocrj.EJ19-0569)

5 Shikuma J, Kan K, Ito R, Hara K, Sakai H, Miwa T, Kanazawa A & Odawara M. Critical review of IgG4-related hypophysitis. *Pituitary* 2017 **20** 282–291. (https://doi.org/10.1007/s11102-016-0773-7)

6 Bando H, Iguchi G, Fukuoka H, Taniguchi M, Yamamoto M, Matsumoto R, Suda K, Nishizawa H, Takahashi M, Kohmura E *et al*. The prevalence of IgG4-related hypophysitis in 170 consecutive patients with hypopituitarism and/or central diabetes insipidus and review of the literature. *European Journal of Endocrinology* 2013 **170** 161–172. (https://doi.org/10.1530/EJE-13-0642)

7 Iseda I, Hida K, Tone A, Tenta M, Shibata Y, Matsuo K, Yamadori I & Hashimoto K. Prednisolone markedly reduced serum IgG4 levels along with the improvement of pituitary mass and anterior pituitary function in a patient with IgG4-related infundibulohypophysitis. *Endocrine Journal* 2014 **61** 195–203. (https://doi.org/10.1507/endocrj.EJ13-0407)

8 Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC & Rose NR. Autoimmune hypophysitis. *Endocrine Reviews* 2005 **26** 599–614. (https://doi.org/10.1210/er.2004-0011)

9 Li Y, Gao H, Li Z, Zhang X, Ding Y & Li F. Clinical characteristics of 76 patients with IgG4-related hypophysitis: a systematic literature review. *International Journal of Endocrinology* 2019 **2019** 5382640. (https://doi.org/10.1155/2019/5382640)

10 Bellastella G, Maiorino MI, Bizzarro A, Giugliano D, Esposito K, Bellastella A & Bellis A. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. *Pituitary* 2016 **19** 625–642. (https://doi.org/10.1007/s11102-016-0736-z)

11 Honegger J, Buchfelder M, Schlaffer S, Droste M, Werner S, Strasburger C, Störmann S, Schopohl J, Kacheva S, Deutschbein T *et al*. Treatment of primary hypophysitis in Germany. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 3460–3469. (https://doi.org/10.1210/jc.2015-2146)

Received in final form 31 May 2021
Accepted 7 June 2021