Two cases of immunoglobulin G4 (IgG4)-related hypophysitis diagnosed without pituitary biopsy

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Abstract

Background: Immunoglobulin G4-related hypophysitis (IgG4-RH) is a rare disease, diagnosis of which typically depends on histopathology following an invasive pituitary biopsy, possibly leading to permanent hypopituitarism. Herein, we report two cases of IgG4-RH with favorable responses to glucocorticoids. One of them was multiple organs involved and treated with glucocorticoids and methotrexate.

Methods: We retrospectively review clinical features, radiological images, and treatment of two cases with IgG4-RH. In addition, literature on IgG4-RH was comprehensively reviewed and a new therapeutic strategy for IgG4-RH was provided.

Results: A 45-year-old man presented with diabetes insipidus for 6 months. Pituitary magnetic resonance imaging (MRI) indicated thickening of pituitary stalk. His serum IgG4 was 13,500 mg/l and hormonal evaluation revealed isolated growth hormone deficiency. Pituitary biopsy was denied by the patient due to fears of permanent pituitary damage. Treatment with prednisone and methotrexate (MTX) for 1 week led to improvement in sellar images and reduction in IgG4 level. His IGF1 (insulin-like growth factor-1) recovered after a 4-month treatment. The second case is a 43-year-old woman presenting with diabetes insipidus and amenorrhea for 20 months. Her pituitary MRI was similar to the patient above. Her serum IgG4 level was 5980 mg/l and hormonal measurement confirmed isolated hypogonadotropic hypogonadism. After 2 weeks of prednisone, the sellar images improved. After 3 months of treatment, her pituitary MRI was normal, IgG4 level had decreased to near normal range, and menstruation resumed. Literature review found additional patients with IgG4-RH, who were treated successfully without invasive pituitary biopsy in a manner similar to our cases. Therefore, we discuss the necessity of invasive pituitary biopsy for IgG4-RH.

Conclusion: For suspected IgG4-RH with pituitary hormone deficiency, biopsy-induced hypopituitarism may be avoided by using diagnostic glucocorticoid treatment. Impaired pituitary hormone secretion may be recovered in response to steroid therapy. Improved pituitary MRI after 1–2 weeks of glucocorticoid treatment may provide diagnostic evidence of IgG4-RH.

Keywords: diagnostic treatment, IgG4-related hypophysitis, pituitary hormones

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Introduction

Immunoglobulin G4-related disease is a chronic and fibrotic inflammatory disease involving multiple organs,[1] including the lacrimal gland, salivary gland, pancreas, bile duct, liver, kidney, and retroperitoneum.[2–4] The main clinical features are elevated serum IgG4 level and IgG4-positive lymphocyte infiltration into tissues. IgG4-related hypophysitis (IgG4-RH), which involves the hypothalamus and pituitary gland, accounts for 1.3% of primary hypophysitis.[5] The incidence ratio of men to women is 3.2:1, and the average age of onset is 66.3 ± 11.5 years.[5] The main pathological features include infiltration of IgG4-positive lymphocytes,

storiform fibrosis, and obstructive phlebitis.[5] Because clinical manifestations of IgG4-RH are non-specific, it is difficult to distinguish from lymphocytic hypophysitis, langerhans cell histiocytosis, and intracranial germ cell tumors. IgG4-RH responds well to glucocorticoid therapy, but difficulty in diagnosis may delay appropriate treatment. We report two cases of IgG4-RH in the Division of Endocrinology from Peking Union Medical College Hospital (PUMCH) with good responses to steroid therapy with or without methotrexate (MTX), in order to provide new insights for diagnosis and treatment of IgG4-RH.

Case description

Case 1

A 45-year-old man presented with polydipsia, polyuria, and weight loss for 6 months. Headache, dizziness, nausea, vomiting, blurred vision, and visual field defect were denied. His body mass index (BMI) was 28.7 kg/m^2 with height of 170 cm and weight of 83 kg. No enlarged lymph nodes or swelling of salivary glands were noted. His past medical history included chronic obstructive pulmonary disease, obsolete tuberculosis, and thymic cyst surgery. He denied any history of autoimmune disease.

Laboratory investigation

Laboratory tests showed lowered urine specific gravity (SG) and hypernatremia. Serum IgG4 was 13,500 mg/l (80–1400), and IgG1, IgG2, and IgG3 were in the normal range. Cerebrospinal fluid pressure was 120 mm H_2O. Routine examination and biochemical tests of cerebrospinal fluid were negative. Tuberculin skin test and T-cell speckle detection was positive. Other laboratory test results are shown in Table 1.

Pituitary hormones

Insulin-like growth factor-1 (IGF1) was low (89 ng/ml). Other hormonal results are shown in Table 1.

Imaging findings

Magnetic resonance imaging (MRI) of the pituitary showed nodule thickening of the upper part of pituitary stalk and loss of the posterior pituitary signal (Figure 1). Ultrasound indicated enlargement of lacrimal glands, and orbital MRI indicated enlargement of extra ocular muscle. Lung and abdominal computer tomography (CT) revealed enlargement of mediastinal lymph nodes and calcified nodules in the abdominal cavity. Evaluation of salivary gland, pancreas, bile duct, liver, kidney, and retroperitoneum did not show any abnormality.

Treatment

Desmopressin, 50 μg twice a day, improved symptoms of polyuria and polydipsia. Prednisone, 30 mg/day, and MTX, 15 mg per week, were administered, due to multiple organ involvement. Alarmed that tuberculosis may relapse with immunosuppression therapy, isoniazid was given 0.3 g per day to prevent tuberculosis relapse. A week later, MRI revealed thinning of the enlarged pituitary stalk; 6 weeks later, serum IgG4 decreased from 13,500 mg/l to 5090 mg/l and pituitary MRI remained stable. His IGF-1 level increased to 230 ng/ml. Follow-up examination showed that enlarged lacrimal glands and extra ocular muscle became smaller in size. Mediastinal lymph nodes did not change. No sign of relapsing tuberculosis was observed.

Case 2

A 43-year-old woman presented with polydipsia, polyuria, amenorrhea, and fatigue for 20 months. Headache was denied. On physical examination, her BMI was 21 kg/m^2 with height of 154 cm and weight of 50 kg. No enlarged lymph nodes were palpable. Her past medical history indicated allergic asthma and penicillin allergy.

Laboratory investigation

Laboratory tests showed lowered urine SG. IgG4 was 5980 mg/l (normal range 80–1400). Other laboratory findings are listed in Table 1. Cerebrospinal fluid pressure was 178 mm H_2O. Routine examination and biochemical tests of the cerebrospinal fluid were negative.

Pituitary hormones

Hormonal tests indicated hypogonadotropic hypogonadism. Other pituitary hormones were in the normal range (Table 1).

Table 1. Laboratory findings and pituitary hormones in case 1 and 2.

Item	Patient 1 (male)		Patient 2 (female)		Normal range
	Baseline	6 weeks	Baseline	3 months	–
LH (IU/l)	2.9	3.1	0.23	1.81	2.2–8.6
FSH (IU/l)	3.2	2.9	2.3	5.8	2.3–9.3
Estrodiol (pg/ml)	20	36	39.7	39	<47 (Male)
					25–160 (Female)
Progesterone (ng/ml)	0.46	–	0.68	1.32	0.10–0.84
Testosterone (ng/ml)	2.85	3.22	1.00	0.78	1.75–7.81 (Male)
					0.10–0.75 (Female)
Prolactin (ng/ml)	7.7	9.3	25	24	2.6–13.1
FT4 (ng/dl)	1.36	1.22	1.18	1.15	0.81–1.89
FT3 (pg/ml)	2.67	2.74	2.80	2.53	1.80–4.10
TSH (μIU/ml)	1.14	2.51	2.3	1.73	0.38–4.34
IGF1 (ng/ml)	89	230	114	135	101–267
GH (ng/ml)	<0.05	1.2	0.1	0.8	<2.0
F (8 a.m.) (μg/dl)	13.8	–	17.0	–	4–22.3
ACTH (8 a.m.) (pg/ml)	28.3	–	23.3	–	0–46
24-h UFC (μg)	37.2	–	42.5	–	12.3–103.5
Urine SG	⩽1.005	1.015	⩽1.005	1.010	1.005–1.030
Serum Na (mmol/l)	146	143	145	138	135–145
Fasting glucose (mmol/l)	5.1	5.7	4.6	4.8	3.9–6.1
WBC ($\times 10^9$/l)	8.96	12.41	7.92	11.7	4–10
EOS (%)	13.8	8.7	4.8	5.2	0.5–5.0
ESR (mm/h)	38	32	15	17	0–20
IgG4 (mg/l)	**13500**	**5090**	**5980**	**1570**	80–1400
IgE (kU/l)	1022	980	149	126	0–60
IgG1 (mg/l)	6210	5960	9680	7425	4900–11400
IgG2 (mg/l)	5770	5370	6910	4362	1500–6400
IgG3 (mg/l)	657	598	555	462	200–1100

ACTH, adrenocorticotropic hormone; EOS, eosinophilia; ESR, erythrocyte sedimentation rate; F, serum free cortisol; FSH, follicle-stimulating hormone; FT3, free triiodogonine; FT4, free thyroxine; GH, growth hormone; IgE, Immunoglobulin E; IGF-1, insulin-like growth factors-1; IgG1, Immunoglobulin G 1; IgG2, Immunoglobulin G 2; IgG3, Immunoglobulin G3; IgG4, Immunoglobulin G 4; LH, luteinizing hormone; SG, specific gravity; TSH, thyrotropin; UFC, urine free cortisol; WBC, white blood cell.

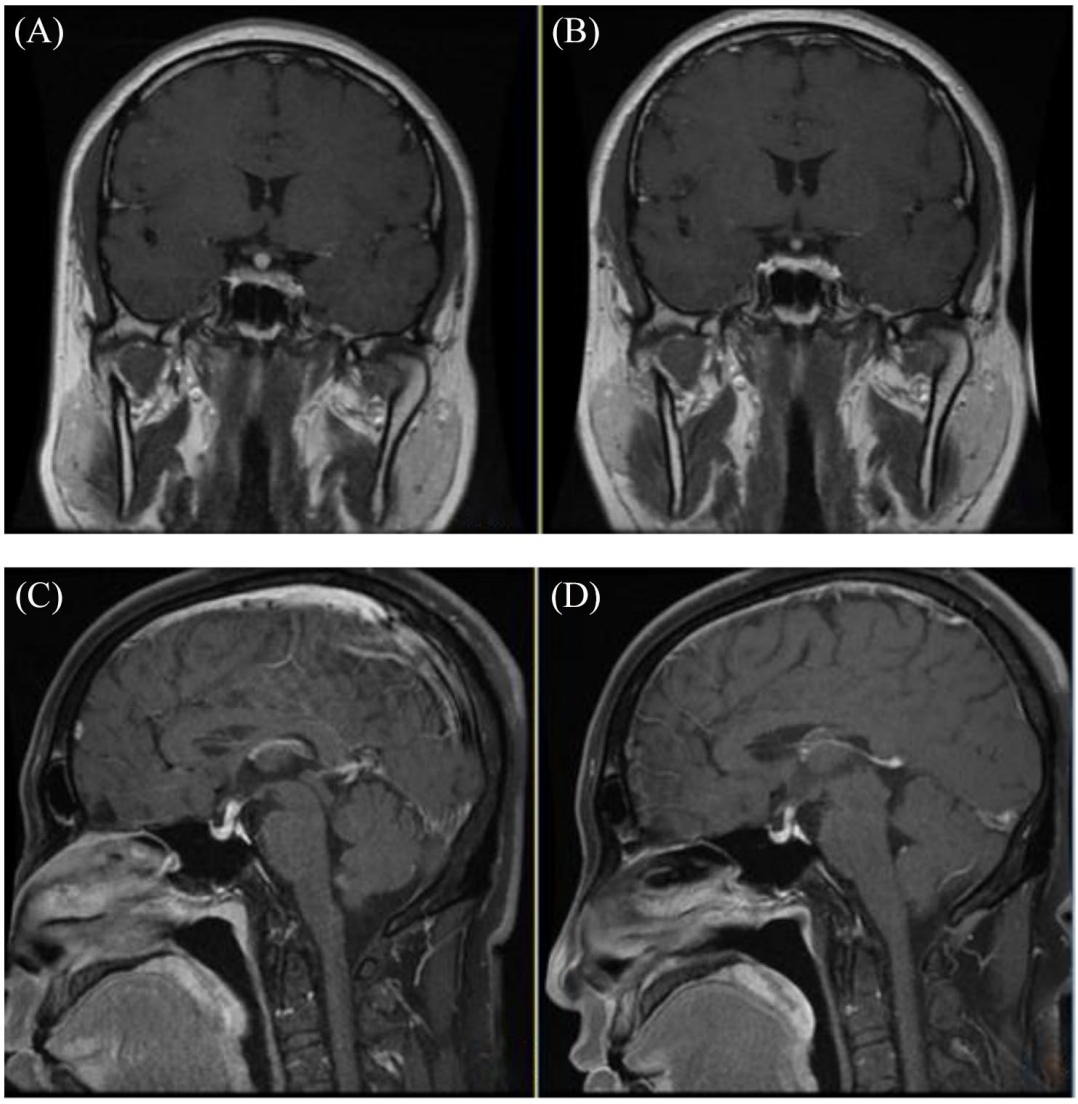

Figure 1. Pituitary MRI showed enlarged pituitary stalk on T1 MRI for case 1 (male, 45 years old). (A) and (C) show nodular thickening of the upper part of pituitary stalk and loss of the posterior pituitary signal on T1 MRI before treatment. (B) and (D) show that the pituitary stalk became thinner 1 week after glucocorticoid and MTX treatment.
MRI, magnetic resonance imaging; MTX, methotrexate.

Imaging findings

Pituitary MRI showed thickening of the upper part of pituitary stalk and loss of the posterior pituitary signal on T1-weighted MRI (Figure 2). Chest CT revealed multiple tiny pulmonary nodules in both lungs, which possess no metabolic activity on ^{18}F-FDG positron emission tomography (PET)-CT. No other abnormality was shown on the PET-CT.

Treatment

Desmopressin was given to improve symptoms of polyuria and polydipsia. Prednisone, 40 mg/day, was administered. At 2 weeks later, MRI showed thinning of the pituitary stalk, and serum IgG4 had decreased from 5260 mg/l to 3580 mg/l; 3 months later, MRI was normal and serum IgG4 had decreased to 1570 mg/l (normal range 80–1400). Her menstruation resumed. Follicle stimulating

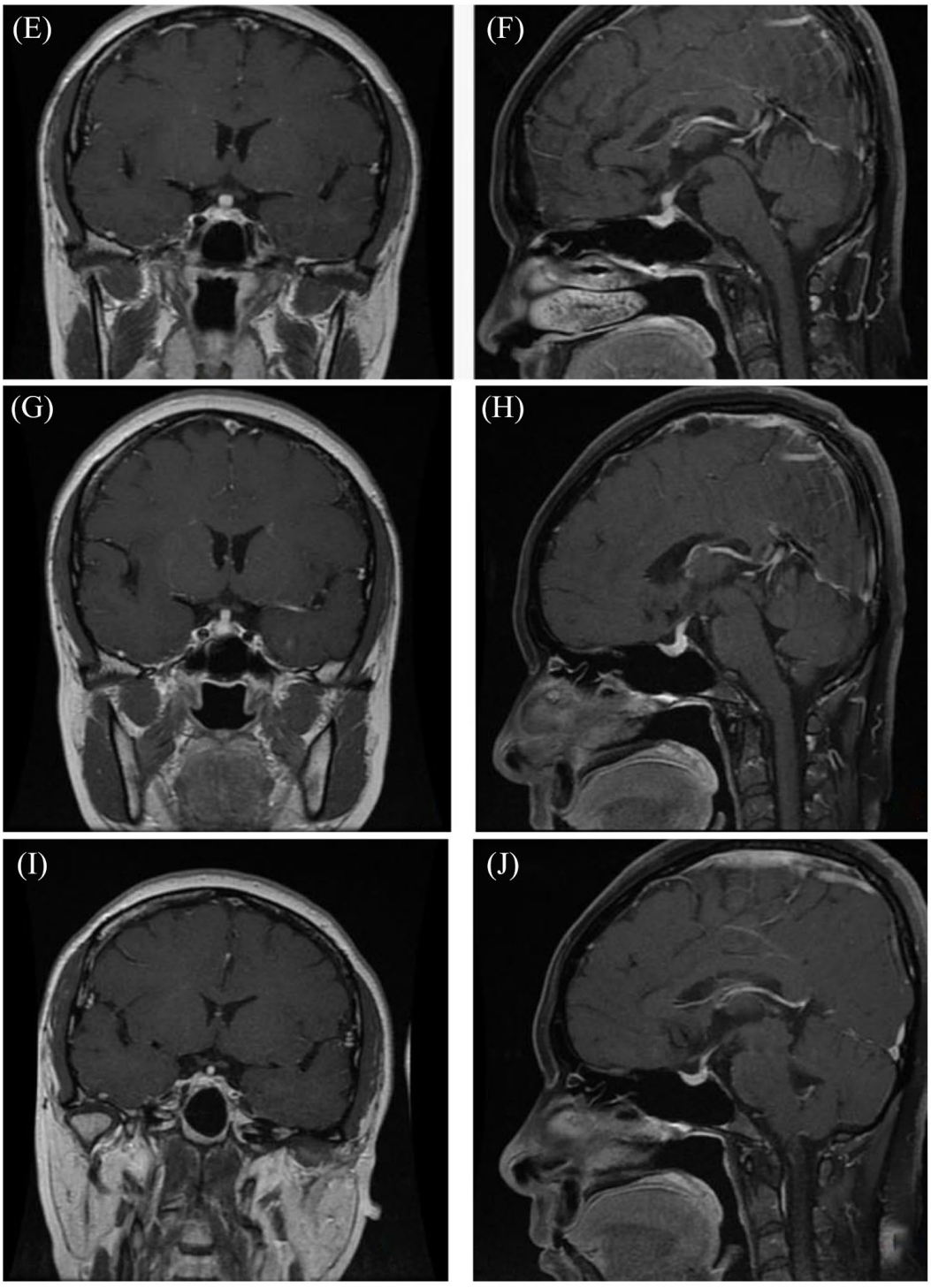

Figure 2. Pituitary MRI for case 2 (female, 43 years old). (E) and (F) show thickening of the upper part of pituitary stalk and loss of the posterior pituitary signal on T1 MRI (December 2018). (G) and (H) show a thinner pituitary stalk 2 weeks after glucocorticoid treatment (11 February 2019). (I) and (J) show that the pituitary stalk recovered to normal 3 months after glucocorticoid treatment (13 May 2019).
MRI, magnetic resonance imaging.

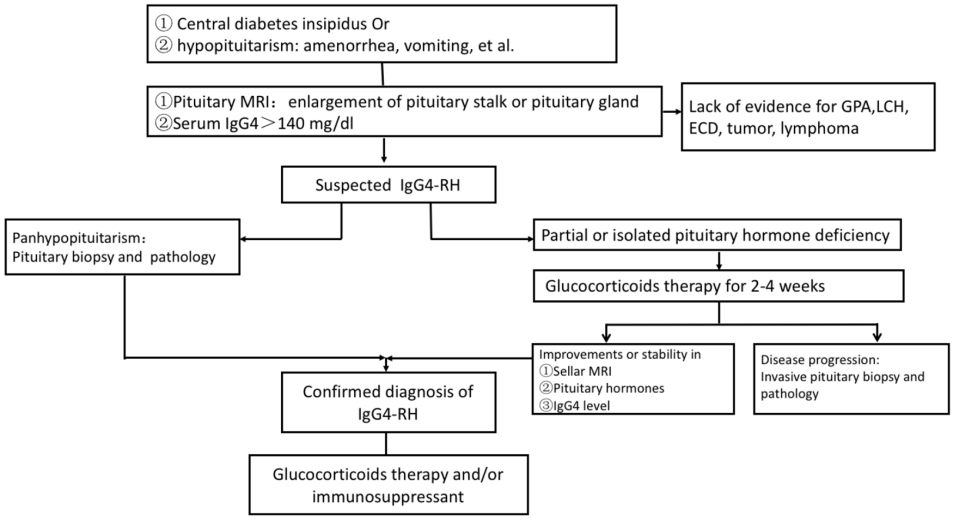

Figure 3. Flow chart for management of patients with suspected IgG4-RH.
ECD, Erdheim-Chester disease; GPA, granulomatosis with polyangiitis; IgG4-RH, immunoglobulin G4-related hypophysitis; LCH, Langerhans cell histiocytosis; MRI, magnetic resonance imaging.

hormone (FSH) level increased to 5.8 IU/l, luteinizing hormone (LH) to 1.81 IU/l, and E2 to 39 pg/ml.

Discussion

IgG4-related disease is an autoimmune disease involving multiple systems that is increasingly recognized.[6] The incidence of IgG4-related disease is 2.8–10.8 per million in Japan. The disease occurs more in the elderly men.[7,8] Clinical features of IgG4-related disease include swelling of one or more organs, elevated serum IgG4 level, IgG4-positive lymphocytes infiltration (IgG4-positive/IgG4-positive＞40%), and prompt response to glucocorticoids.[5,9–11]

IgG4-RH, defined as IgG4 positive lymphocyte infiltration to the hypothalamus-pituitary area, presents primarily with central diabetes insipidus and other nonspecific symptoms, such as fatigue and weight loss.[12] IgG4-RH can be diagnosed in three ways, as proposed by Leporati in 2011.[12] First, pituitary histopathology is the gold standard for diagnosis. Second, pituitary MRI and histopathology from other organs may be used for diagnosis.[13,14] Third, if histopathology of other organs is not available, a combination of pituitary MRI, increased serum IgG4, and prompt response to glucocorticoid therapy, would lead to the diagnosis.[12] Our patients could be diagnosed with IgG4-RH according to the third criterion.

Most patients with IgG4-RH have a favorable response to glucocorticoids.[5] In our cases, prednisone 30–40 mg/day (equal to 0.5–0.6 mg/kg/day) was administered, as recommended.[12,15] After 1–2 weeks of treatment, pituitary MRI improved. After 1–3 months, serum IgG4 level had decreased significantly. We observed increased IGF-1 level in the male patient and resumed menstruation in the female patient, indicating that glucocorticoid therapy may restore pituitary function in IgG4-RH. Literature review on IgG4-RH found that steroid therapy was effective in 69 of 71 cases (97.2%) at decreasing pituitary size. Among them, 21 cases were diagnosed by elevated IgG4 level and pituitary MRI, without invasive pituitary biopsy.[5] Based on the above evidence, we propose that glucocorticoid therapy for suspected IgG4-RH patients with only partial or isolated pituitary hormone deficiency, thus avoiding pituitary biopsy-induced hypopituitarism in these patients.

Addition of immunosuppressant to glucocorticoid in treatment for IgG4-RH is still controversial, and it is thought to be helpful in the following situations[16]: (1) Full dosage of glucocorticoid could not prevent disease progression; (2) recurrence on small doses of glucocorticoid maintenance; or (3) patients with multiple organ involvement or extremely high level of IgG4.[16,17] MTX is an immunosuppressant used widely due to its high effectiveness, minimal side effects, and low price.[18] In our male patient, multiple organs were involved and MTX was given.

Diagnosis of IgG4-RH is difficult due to lack of specific clinical manifestations; 30% of hypophysitis and 4% of hypopituitarism is caused by IgG4-RH.[19,20] Another retrospective study found that 41.4% of patients initially diagnosed as lymphocytic hypophysis eventually meet the diagnostic criteria of IgG4-RH.[21] Lymphocytic hypophysitis is more often seen in women late in pregnancy and early postpartum.[21] Recover of menstruation responding to prednisone, as seen in our female patient, is rarely seen in lymphocytic hypophysitis. To date, limited cases of IgG4-RH have been reported, and evidence for its diagnosis and treatment is insufficient. Therefore, two cases with clinically diagnosed IgG4-RH add valuable evidence for disease management. A flow chart for management of IgG4-RH is proposed in Figure 3.

In conclusion, isolated pituitary hormone deficiency could be restored by glucocorticoid therapy in patients with clinically suspected IgG4-RH. Therefore, in patients who respond well and rapidly to glucocorticoid therapy, biopsy could potentially be avoided, which would avoid iatrogenic damage from biopsy including permanent hypopituitarism. Improvement in pituitary MRI and IgG4 level, after 1–2 weeks of steroid therapy, may provide some evidence for the diagnosis of IgG4-RH.

Author Contribution(s)

Wanlu Ma: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing-original draft.

Xueyan Wu: Conceptualization; Funding acquisition; Writing-review & editing.

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Min Nie: Methodology; Writing-review & editing.

Junling Fu: Investigation; Writing-review & editing.

Jiangfeng Mao: Conceptualization; Data curation; Funding acquisition; Writing-review & editing.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Statement for consent

Written informed consent for publication of the patient information was obtained from both patients.

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