Histopathological findings in the landscape of IgG4-related pathology in patients with pituitary dysfunction: Review of six cases

Lilian Vasaitis1 | Johan Wikström2 | Sengul Ahlström3,4 | Olafur Gudjonsson5 | Eva Kumlien5 | Britt Edén Engström6 | Olivera Casar-Borota3,4

1Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden
2Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
3Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
4Department of Clinical Pathology, Uppsala University Hospital, Uppsala, Sweden
5Department of Neuroscience, Uppsala University, Uppsala, Sweden
6Department of Medical Sciences, Endocrinology and Mineral Metabolism, Uppsala University, Uppsala, Sweden

Abstract

IgG4-related hypophysitis (IgG4-RH) is increasingly being reported as an isolated entity or, less frequently, as a manifestation of a multiorgan IgG4-related disease (IgG4-RD), in which typical histopathology is a cornerstone for the diagnosis. We aimed to describe the histopathological changes in the surgical specimens from patients with clinical signs of pituitary disease that fulfilled the current diagnostic criteria for IgG4-RH. Histopathological features were correlated with clinical and radiological findings. Of 19 patients with pituitary dysfunction and inflammatory changes in the surgical pituitary specimen operated on during 2011-2019, we identified five patients with typical IgG4-related pathology (lymphoplasmacytic infiltration with more than 10 IgG4-positive plasma cells per one high power microscopic field, representing at least 40% of all plasma cells and at least focal storiform fibrosis). One patient with diabetes insipidus and pachymeningitis with IgG4-related changes in a biopsy from the dura was also included. Additional histopathological changes that typically are not part of the IgG4-RH were observed: Rathke's cleft cyst in four and granulomatous changes in two patients. One patient had an elevated serum IgG4 level and systemic manifestations that could be associated with the systemic IgG4-RD. Our findings indicate that pure IgG4-RH is uncommon. All patients with pituitary dysfunction, beyond typical IgG4-related pathology, had other pathological findings that could trigger the secondary IgG4-response. Both primary pathology and secondary IgG4-related features should be reported in patients with pituitary dysfunction because their co-occurrence may cause atypical clinical and imaging features, and unexpected response to surgical and pharmacological treatment. The current criteria for the diagnosis of IgG4-RH can lead to overdiagnosis of IgG4-RH if additional pathological changes are not taken into consideration. The classification criteria of IgG4-RD proposed by the American College of Rheumatology/European League Against Rheumatism could help classify patients more properly as IgG4-RH if applied to the pituitary gland.

Keywords

IgG4-related hypophysitis, pituitary inflammation, Rathke's cleft cyst
IgG4-related disease (IgG4-RD) is a multiorgan chronic fibroinflammatory disease with a broad spectrum of clinical manifestations related to IgG4-mediated immune dysregulation. The most prevalent manifestations are submandibular salivary adenitis, dacyroadenitis, autoimmune pancreatitis and retroperitoneal fibrosis. However, any organ can be affected, including the pituitary gland. The main histological features, such as lymphoplasmacytic infiltration with a high proportion of IgG4-bearing plasma cells, usually in admixture with some eosinophils, storiform fibrosis and occasional obliterator phlebitis, are common for all organs, although organ-specific variations may occur. Inflammation and fibrotic reaction result in a tumour mass in the affected organ and frequent organ dysfunction.

Histopathological analysis of the biopsy specimen combined with immunohistochemical analysis by using antibodies toward IgG4 and IgG plasma cells is a cornerstone in the diagnosis of IgG4-RD. Because the IgG4+ plasma cells can occur in a significant number in different pathological conditions and can vary from organ to organ, requirements regarding the number of IgG4+ plasma cells and the ratio between the IgG4+ plasma cells and a total population of IgG+ cells are included in the diagnostic criteria. Histopathological diagnosis may be challenging in advanced phases of the disease when fibrosis is prominent and inflammatory cell infiltration is sparse. Elevated serum IgG4 levels may be useful, although it is not a reliable diagnostic marker of the disease. Careful multidisciplinary correlation of histopathological, serological, clinical and imaging findings improves IgG-RD diagnostic accuracy in an individual patient. Pituitary involvement based on clinical and imaging grounds has previously been reported in patients with systemic IgG4-RD. Soon after, in 2007, the first biopsy-proven case of IgG4-related hypophysitis (IgG4-RH) in a patient with the systemic IgG4-RD was published. In 2011, Leporati et al. proposed the criteria for the diagnosis of IgG4-RH and emphasised the importance of histopathological proof of the disease, putting it as a single criterion sufficient for diagnosis. As the entity became better known among physicians, an increasing number of cases have been reported. However, only about 30 of the published cases of IgG4-RH so far have been histologically confirmed in pituitary biopsy. Thus, the whole spectrum of IgG4-related histopathological changes in the pituitary gland and sellar region is still unknown.

Leporati et al. suggested the presence of more than 10 IgG4+ plasma cells per high power field (HPF) as histological evidence of the IgG4-RH. According to the Consensus statement on the pathology of IgG4-RD, the pathological diagnosis of IgG4-RD requires the presence of two of the three major histopathological features: (i) dense lymphoplasmacytic infiltrate with an increased number of IgG4+ plasma cells; (ii) fibrosis with at least focal storiform pattern; and (iii) obliterator phlebitis. Although the cut-off for the number of IgG4+ plasma cells required for diagnosis varies in different organs, the IgG4+/IgG+ ratio of more than 40% is recommended for all organs. Histological criteria including the presence of more than 10 IgG4+ cells per HPF and IgG4+/IgG+ ratio of more than 40% are also included in the clinical guidelines for the diagnosis of IgG4-RH by the Japan Endocrine Society. Recently, the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) published a more complex set of inclusion and exclusion criteria for the classification of IgG4-RD in the frequently affected organs, not including the pituitary gland.

In the present study, we aimed to describe the histopathological changes in the surgical specimens from patients with clinical signs of pituitary disease that fulfilled the criteria for IgG4-RH. Histopathological features were correlated with clinical and radiological findings. We discuss the potential triggers of IgG4-inflammatory response and the clinical and diagnostic impacts of IgG4-related changes in patients with pituitary involvement.

2 | MATERIALS AND METHODS

2.1 | Selection of clinical cases

In total, 19 patients operated on during the period 2011-2019 with inflammatory changes of any type in pituitary specimens, and one patient with pituitary dysfunction and inflammation in the dura, were identified through the search in the local pathology database. All the specimens were re-evaluated. In six cases with lymphoplasmacytic infiltration and fibrosis, suggestive of the IgG4-related process, additional immunohistochemical analyses were performed. The specimens were evaluated to confirm that the cases fulfilled both the criteria of Leporati et al. for IgG4-RH (> 10 IgG4+ plasma cells per HPF) and the international guidelines for the diagnosis of IgG4-RD (dense lymphoplasmacytic infiltration with an increased number of IgG4 immunoreactive cells, representing at least 40% of all plasma cells, fibrosis with at least focal storiform character). The remaining 14 patients with pituitary specimens without the IgG4-related changes were excluded. In these patients, lymphocytic hypophysitis was diagnosed in three cases, granulomatous inflammation without additional pathology in two cases, lymphocytic inflammation secondary to a cystic process in six cases and granulomatous inflammation secondary to a cystic process in three cases. The cystic process represented Rathke’s cleft cyst in four cases, craniohypophyngioma in one case and epithelial fragments that could not be classified more specifically in four cases.

The study was approved by the Regional Ethical Committee in Uppsala (Dnr 2016/126). All six patients with IgG4-related pathology presented here signed the informed consent to participate in the study.

2.2 | Histopathological and immunohistochemical analyses

In six cases with IgG4-related features suspected in routine haematoxylin and eosin stained sections, immunohistochemical
analyses were performed with the antibodies: CD3 (polyclonal, article number R503/GA503; DAKO, Glostrup, Denmark; ready-to-use), CD20 (monoclonal, clone L26, article number IR604/GA604; DAKO; ready-to-use), CD4 (monoclonal, clone 4B12/SP35, article number IR649/790-4423; DAKO; ready-to-use), CD138 (monoclonal, MI15, article number IR642; DAKO; ready-to-use), IgG (polyclonal, article number A0423; DAKO; dilution 1:3000) and IgG4 (monoclonal, clone HP6025, article number GTX78419; MediQip; dilution 1:50). All immunohistochemical analyses were performed in DAKO-Autostainer according to the standard protocols used at the clinical diagnostic laboratory for immunohistochemistry at the Department of Clinical Pathology, Uppsala University Hospital.

2.3 | Clinical data and laboratory analysis

Detailed clinical data regarding the patients’ age, gender, clinical symptoms, results of the relevant laboratory tests, and response to surgical and pharmacological therapy were collected from the electronic patient records.

2.4 | Magnetic resonance imaging (MRI) work-up

Magnetic resonance images before and after surgery for each patient were re-examined by an experienced neuroradiologist (JW). MRI examinations were performed at different hospitals and with slightly different techniques. In the five cases with sellar pathology (patients 1-5), all examinations included T1-weighted turbo-spin-echo sequences before and after gadolinium administration in the coronal and sagittal planes, as well as T2-weighted turbo-spin-echo sequence in the sagittal or coronal plane. The slice thickness varied between two and four millimeters. Four patients were examined at 1.5 T (patients 1-4) and one at 3 T (patient 5). In the case of pachymeningitis (patient 6), the examination was performed at 3 T using a routine brain protocol, with the diagnosis mainly based on 3D T1-weighted TSE imaging after gadolinium administration. MRI examinations before surgery and post-surgical MRIs, including the last available examination, were evaluated. The pituitary mass lesion size is reported in three dimensions (depth x width x height).

2.5 | Surgery

All patients with pituitary mass underwent transsphenoidal pituitary surgery (TSS) by an experienced neurosurgeon (OG). The main indication for surgery was a space-occupying pituitary mass that compromised visual functions. One patient who had headaches, diplopia and pituitary dysfunction without identifiable sellar mass lesion, and subsequently developed pachymeningitis, underwent only a limited surgical procedure to obtain a meningeal biopsy.

3 | RESULTS

3.1 | Histopathological results

In all six specimens, five from the pituitary gland and one from the dura, the diagnostic criteria for IgG4-RH, as defined by Deshpande et al and Leporati et al, were fulfilled. All patients had prominent fibrosis, focally of storiform character, and rich inflammatory cell infiltrate composed of CD138+ and IgG+ plasma cells, CD3+ T-lymphocytes, CD4+ T helper cells, CD68+ macrophages and CD20+ B-cells with the admixture of scattered eosinophils. IgG4+ plasma cells varied in number from 30 to more than 50 cells per HPF and represented at least 40% of all CD138+ plasma cells in the respective foci. Obliterated blood vessels were observed in one specimen; however, the presence of obliterated blood vessels was generally difficult to assess as a result of extensive fibrosis. Moreover, additional pathological lesions, not typically associated with IgG4-RD, were observed in all patients: Rathke’s cleft cyst in three patients, epithelial fragments with amorphous material suspected for Rathke’s cleft cyst in one patient and granulomatous process in two patients. The histological features and presence of IgG4+ plasma cells are shown in Figure 1.

3.2 | Demographics and clinical histories of the patients

The age of the patients at the onset of the symptoms ranged from 38 to 71 years. Among those, four were women and two men. The most frequent presenting symptoms were headache, diabetes insipidus, visual disturbances and decreased libido or amenorrhea. The surgery biopsies were performed within 2-60 months after the onset of the symptoms. Before surgery, serum IgG4 levels were performed only in patient 4, and anti-neutrophil cytoplasmic antibody (ANCA) serology only in patient 6. After surgery, serum IgG4 levels were controlled in all patients, and ANCA serology was tested in three patients. The patients underwent surgery because of suspected pituitary adenoma/tumor or suspected sarcoidosis. After biopsy results, four patients (patients 2-5) were diagnosed with IgG4-RH, of whom one patient (patient 4) had a systemic IgG4-RD. Patient 1 was diagnosed with granulomatosis with polyangiitis (GPA) despite concomitant typical IgG4-related histopathology. Patient 6, who, besides IgG4-related pathology, showed necrotising granulomas in the meningeal biopsy, was diagnosed with chronic pachymeningitis, which could be IgG4 and/or sarcoidosis-related.

The details of clinical, laboratory and treatment data are outlined below and in Table 1.

3.3 | Patient 1

A 38-year-old female developed a worsening headache that required an MRI examination demonstrating a large intra- and suprasellar
lesion (14 × 17 × 17 mm), causing upward dislocation of the optic chiasm. The signal intensity pattern is compatible with a solid process with partially high fluid content. 2A, Coronal contrast medium enhanced T1-weighted MRI shows a bilobal peripherally enhancing lesion, with intra- and suprasellar components, with the latter causing upward dislocation of the optic chiasm. The central portions have signal intensity characteristics suggesting fibrosis. 3A, Coronal T2-weighted image shows a predominantly suprasellar cystic lesion, with oedema in the adjacent optic chiasm. 4A, Coronal T2-weighted image shows a cystic lesion occupying a large part of the pituitary gland, causing slight upward bulging but without affection of the optic chiasm. 5A, Coronal T2-weighted image shows a large intra- and suprasellar lesion with high water content. 6A, Sagittal contrast medium enhanced T1-weighted MR image shows thickening and enhancement of the dura anterior to the brain stem. 1B – 6B, Rich lymphoplasmacytic infiltration admixed with eosinophils and fibrosis were present in all the cases (haematoxylin and eosin, ×200). 1C – 6C, More than 30 IgG4+ cells/HPF (IgG4 IHC, ×200) were present in all the specimens. 1 – 6 D, E, Additional lesions not typical for IgG4-RD have been observed in all the patients. Necrotising granulomas with occasional multinuclear giant cells were present in patients 1 and 6 (1D, 6D). Features consistent with Rathke’s cyst, such as epithelial fragments (2D, 3D, 4D, 5D) and accumulation of eosinophilic amorphous material suspected for cyst content (2E, 4E), were observed in patients 2-5 (haematoxylin and eosin, ×200 except for 5D, which has a magnification of ×100). Microphotograph 3C has been reprinted with a different magnification from the Encyclopedia of Endocrine Diseases (Figure 5D, p. 333) with permission from Elsevier (license number 4858250707676, license date 29 June 2020).

Histopathological examination demonstrated typical IgG4-related features and additional scattered necrotising granulomas with occasional multinuclear giant cells. No microbial agents were demonstrated using Ziehl-Neelsen, Gram, periodic acid-Schiff (PAS) and Grocott silver staining.

Additional laboratory work-up demonstrated a high positivity for proteinase 3 (PR3)-ANCA (> 160 kE L⁻¹; ref. < 20 kE L⁻¹) and a slightly increased C-reactive protein (CRP) (23; ref. < 5 mg L⁻¹). Serum IgG4 measured during the Prednisolone treatment was 0.31 (ref. < 1.25 mg L⁻¹) and the angiotensin-converting enzyme (ACE) test for sarcoidosis was negative. Computerised tomography (CT) of the thorax revealed suspected granuloma in the right lung’s middle lobe. The patient was diagnosed with GPA and treated initially for the first 3 days with methylprednisolone and later on with prednisolone, azathioprine and rituximab. Treatment resulted in a gradual normalisation of the ANCA levels and a regress of the lung lesion. Visual fields normalised after the surgery. Postoperative pituitary MRI demonstrated a large sellar mass (12 × 10 × 10 mm) that gradually decreased and was no longer seen on MRI examinations conducted 2 and 4 years after surgery. The patient is currently in remission with azathioprine 150 mg daily as maintenance therapy and substitution therapy for hypopituitarism.

3.4 | Patient 2

A 42-year-old male was admitted to hospital because of headaches. Additionally, he complained of frequent urination and impaired libido.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age at onset of the symptoms/age at surgery (years)</td>
<td>38/38</td>
<td>38/43</td>
<td>55/59</td>
<td>69/69</td>
<td>71/72</td>
<td>57/59</td>
</tr>
<tr>
<td>Pre-surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary-related symptoms</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>Headache</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Amenorrhea</td>
<td>Decreased libido</td>
<td>Decreased libido</td>
<td>Decreased libido</td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Visual disturbances</td>
<td></td>
<td>Visual disturbances</td>
</tr>
<tr>
<td></td>
<td>Visual disturbances</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapituitary manifestations</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Rhinoconjunctivitis</td>
<td>None</td>
<td>Pachymeningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic asthma</td>
<td></td>
<td>Ground glass opacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung fibrosis</td>
<td></td>
<td>Intermittent abducens nerve palsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td>Serology tests</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>s-IgG4 increased</td>
<td>Not done</td>
<td>MPO-ANCA+</td>
</tr>
<tr>
<td>Hormone deficiencies</td>
<td>ADH</td>
<td>ADH</td>
<td>ADH</td>
<td>ACTH</td>
<td>TSH</td>
<td>ADH</td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
<td>TSH</td>
<td>ACTH</td>
<td>TSH</td>
<td>FSH/LH</td>
<td>TSH</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>FSH/LH</td>
<td>FSH/LH</td>
<td>FSH/LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substitution</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Hydrocortisone</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>Thyroxine</td>
<td>Thyroxine</td>
<td>Hydrocortisone</td>
<td>Thyroxine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thyroxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substitution</td>
<td>None</td>
<td>None</td>
<td>Desmopressin</td>
<td>Thyroxine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thyroxine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-surgery diagnosis</td>
<td>Pituitary adenoma</td>
<td>Pituitary adenoma or craniopharyngioma</td>
<td>Pituitary adenoma or sarcoidosis</td>
<td>Pituitary adenoma or craniopharyngioma</td>
<td>Pituitary adenoma</td>
<td>Suspected meningeal sarcoidosis</td>
</tr>
<tr>
<td>Anti-inflammatory therapy</td>
<td>None</td>
<td>None</td>
<td>Glucocorticoids</td>
<td>Methotrexate</td>
<td>None</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NSAID</td>
</tr>
<tr>
<td>Post-surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remaining symptoms</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>Diabetes insipidus</td>
<td>None</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Amenorrhea</td>
<td>Decreased libido</td>
<td>Decreased libido</td>
<td>Decreased libido</td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Visual disturbances</td>
<td></td>
<td>Visual disturbances</td>
</tr>
<tr>
<td></td>
<td>Visual disturbances</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapituitary manifestations</td>
<td>Suspected granuloma in the lung</td>
<td>None</td>
<td>Seizures</td>
<td>Rhinoconjunctivitis</td>
<td>None</td>
<td>Pachymeningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-specific lung lesions</td>
<td>Allergic asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrent pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology tests</td>
<td>s-IgG4 normal</td>
<td>s-IgG4 normal</td>
<td>s-IgG4 normal</td>
<td>s-IgG4 increased</td>
<td>s-IgG4 normal</td>
<td>s-IgG4 normal</td>
</tr>
<tr>
<td></td>
<td>PR3-ANCA+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone deficiencies</strong></td>
<td>ADH</td>
<td>ADH</td>
<td>ADH</td>
<td>ADH</td>
<td>ACTH</td>
<td>ADH</td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
<td>ACTH</td>
<td>ACTH</td>
<td>ACTH</td>
<td>TSH</td>
<td>TSH</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>TSH</td>
<td>TSH</td>
<td>TSH</td>
<td>FSH/LH</td>
<td>FSH/LH</td>
</tr>
<tr>
<td></td>
<td>FSH/LH</td>
<td>FSH/LH</td>
<td>FSH/LH</td>
<td>FSH/LH</td>
<td>GH</td>
<td>GH</td>
</tr>
<tr>
<td><strong>Substitution</strong></td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
<td>Desmopressin</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>Hydrocortisone</td>
<td>Hydrocortisone</td>
<td>Hydrocortisone</td>
<td>Hydrocortisone</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td>Thyroxine</td>
<td>Thyroxine</td>
<td>Thyroxine</td>
<td>Thyroxine</td>
<td>Thyroxine</td>
<td>Thyroxine</td>
</tr>
<tr>
<td></td>
<td>Estrogen</td>
<td>Estrogen</td>
<td>Estrogen</td>
<td>Estrogen</td>
<td>Testosterone</td>
<td>Testosterone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td>GPA</td>
<td>IgG4-RH</td>
<td>IgG4-RH</td>
<td>IgG4-RH</td>
<td>IgG4-RH</td>
<td>Chronic pachymeningitis</td>
</tr>
<tr>
<td><strong>Anti-inflammatory therapy</strong></td>
<td>Glucocorticoids</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rituximab</td>
</tr>
</tbody>
</table>

*Note:* Patients 1-4 and 6 had clear symptoms of diabetes insipidus.

Patients 1, 4 and 5 had low morning cortisol levels pre-surgery and were still clinically considered ACTH deficient post-surgery.

Patient 2 had low IGF-1 pre-surgery and was evaluated with GHRH/arginine and ACTH stimulation test post-surgery.

Patient 3 developed severe iatrogenic Cushing’s syndrome, whereas true ACTH deficiency could not be evaluated.

Patients 4 and 5 had IGF-1 values post-surgery below the reference range for age.

**Abbreviation:** ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GPA, granulomatosis with polyangiitis; IgG4-RH, IgG4-related hypophysitis; LH, luteinising hormone; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; NSAID, nonsteroidal anti-inflammatory drug; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibody; TSH, thyroid-stimulating hormone.
5 years back. Initial laboratory tests revealed low testosterone and insulin-like growth factor (IGF)-1 levels. Thyroid hormones and cortisol levels were normal. He had bitemporal visual field defects and impaired visual acuity. MRI work-up showed a bilarbar peripherally enhancing lesion (14 × 13 × 16 mm) with intra- and suprasellar components, the latter causing upward dislocation of the optic chiasm. The central portions had signal intensity characteristics, suggesting fibrosis. The mass lesion contained bleeding and was calcified, thus, raising a suspicion of a craniopharyngioma.

TSS was performed with the excision of the intrasellar part of the lesion. Histopathological examination demonstrated IgG4-related pathological changes combined with amorphous proteinaceous content and fragments of the ciliated cylindric epithelium, suggestive of Rathke’s cleft cyst.

Visual defects normalised 2 months after the surgery. Stimulation tests confirmed deficiencies of growth hormone and cortisol. Postoperative MRI showed a residual suprasellar component with central calcification and peripheral contrast enhancement that descended to the sella and slowly increased to 12 × 14 × 13 mm during the 5 years of follow-up, resulting in slight chiasma compression.

The patient underwent a second surgery as a result of the slight re-growth of the lesion. The histological picture in the second specimen was dominated by fibrosis. The inflammatory cell infiltration was less cellular than the specimen from the first surgery, and no epithelial structures were identified. Serum IgG4 levels, as well as antinuclear antibody, ACE and CRP tests, were normal. 18F-fluorodeoxyglucose positron emission tomography confirmed no lesions in the other organs. The follow-up with regular MRI examinations has not shown any signs of re-growth of the sellar lesion. The patient remains on substitution therapy because of panhypopituitarism.

### 3.5 Patient 3

A 55-year-old female with a previous history of postpartum diabetes mellitus developed weight gain, increased thirst, decreased appetite, dry skin, loss of hair and decreased libido consistent with diabetes insipidus, hypothyroidism and hypogonadism, which were confirmed by laboratory tests and replaced with thyroxine and desmopressin. IGF-1 and cortisol levels were normal at diagnosis. The MRI revealed a cystic suprasellar lesion (11 × 11 × 12 mm) with contrast-enhancing rim, upward dislocation of the optic chiasm and oedema in the chiasm. The symptoms worsened, being dominated by severe headache, fever, neck stiffness and rapid onset of visual field defects. There were inflammatory markers (pleocytosis with lymphocytosis and monocytosis, and elevated protein) in the cerebrospinal fluid; therefore, neurosarcoidosis was suspected. The patient was treated with high-dose betamethasone, which resulted in rapid improvement of the visual symptoms. Later, betamethasone was changed to prednisolone and combined with methotrexate. The patient developed severe iatrogenic glucocorticoid-related Cushing’s syndrome and hyperglycaemia that required treatment with insulin. Because of the lack of response to the anti-inflammatory therapy and side-effects of methotrexate, the patient received proton beam therapy. After proton therapy, total hypopituitarism developed, and the patient had sporadic intensive headaches. MRI work-ups 1 and 2 years after the proton therapy demonstrated a slow increase of the cystic expansive suprasellar lesion. The lesion’s infundibular part compressed the optic chiasm and the right optic nerve and could not be separated from the pituitary stalk.

As a result of the suprasellar mass’s persistent symptoms and progression despite anti-inflammatory treatment and radiotherapy, the patient underwent TSS 4 years after the symptom onset. The specimen from the pituitary demonstrated Rathke’s cleft cyst surrounded by adenoxyphophysial tissue with typical IgG4-related changes. Postoperatively, visual symptoms improved. However, the patient still has severe cushingoid habitus, fluctuating, occasionally severe headaches, and symptoms of diabetes insipidus. She also developed seizures and non-specific, probably atelectatic, lung lesions. MRI performed 6 months after the surgery showed a suspected small remaining solid contrast-enhancing lesion adjacent to the pituitary stalk, but no remaining cystic suprasellar component. However, there was no evidence of the remaining pituitary lesion at the latest MRI performed recently without a contrast agent. Postoperatively, she has no anti-inflammatory treatment, but remains on hormone replacement therapy.

### 3.6 Patient 4

A 69-year-old male had at least 4 years of history of allergic asthma and rhinoconjunctivitis treated with local corticosteroids and 2-year history of mild bilateral lung fibrosis before he developed diabetes insipidus, fatigue, weight increase and reduced libido. Laboratory tests corresponded to the hypopituitarism that required multi-hormonal substitution. MRI work-up demonstrated a cystic lesion (11 × 13 × 14 mm) in the central part of the pituitary gland, with a small suprasellar part and affection of infundibulum, without chiasma compression or parasellar growth. An MRI performed 6 months later showed a progression of the lesion to 13 × 13 × 17 mm, with contrast enhancement along the pituitary stalk, raising suspicion of sarcoidosis, which could not be confirmed by clinical and laboratory investigation. As a result of the sellar-lesion’s progression, the patient underwent TSS 10 months after the symptom onset. Histopathological evaluation revealed a rich amount of proteinaceous content and Rathke’s cyst epithelium in a landscape typical of IgG4-RD.

Postoperatively, the patient developed recurrent pancreatitis with increased serum pancreatic amylase. The serum IgG4 was elevated before the pituitary surgery (1.46 g L⁻¹; ref. < 1.25 g L⁻¹), then normalised to 0.83 g L⁻¹ 3 months later without any anti-inflammatory treatment, and increased slightly again to 1.22 g L⁻¹ 6 months after surgery, remaining within the normal range at the later follow-up.

At the 1-year MRI control, the pituitary gland had normal size with slightly decreased contrast enhancement than the normal
gland, which was quite suggestive of fibrosis. There were slight signal changes in the optic chiasm and tracts, corresponding to preoperative enhancement areas, possibly representing gliosis.

After the surgery, the patient was treated with hormone substitution because of persistent panhypopituitarism. His lung fibrosis progressed, despite the treatment with an anti-fibrotic drug pirfenidone. He died 4 years after the pituitary surgery at the age of 73.

3.7 | Patient 5

A 71-year-old female with a history of left-sided amblyopia since childhood and well-controlled hypertension and hypercholesterolemia in adult age developed intense headache and vomiting. CT revealed a partly cystic sellar and suprasellar tumorlike lesion, which was touching the optic chiasm. An MRI showed a large intra- and suprasellar lesion (12 × 12 × 4 mm) with high water content, but very low contrast enhancement, compatible with fibrosis. Laboratory tests demonstrated hyponatraemia and low cortisol, thyroxine and gonadotrophin levels requiring substitution therapy. As a result of severe intermittent headaches, the patient underwent TSS. The surgical specimen revealed IgG4-related pathology and Rathke’s cleft cyst.

After the surgery and during hydrocortisone substitution, laboratory tests showed normal serum IgG4, IgG, C3 and C4 complement components, and normal eosinophilic count. Six months after the surgery, an MRI demonstrated a cystic (6 × 3 × 4 mm) lesion along the pituitary gland’s upper surface with rim contrast enhancement interpreted as a residual cyst. The lesion was not identifiable at 1.5-year postoperative control. Two years after the surgery, prolactin slightly increased and, 4 years later, the patient still has hormonal substitution with hydrocortisone, thyroxine and recently added growth hormone.

3.8 | Patient 6

A 57-year-old female with a history of almost 20 years of recurrent diffuse body aches and cholecystitis developed intermittent abducens paresis with normal CT brain findings. Two years later, she experienced headaches, tinnitus, fatigue, obstructive respiratory symptoms and repeated episodes with fever. Laboratory tests showed increased CRP and liver enzymes. The cerebrospinal fluid analysis revealed a non-specific inflammatory reaction with mild monocytosis and elevated proteins. Initially, serum myeloperoxidase-ANCA was positive in low titres. However, repeated autoimmunity, ACE and other tests to rule out infection were negative. Liver biopsy showed signs of fatty liver disease. Chest X-ray examination showed transient discreet ground glass phenomenon. Differential diagnoses of GPA, Sjögren syndrome and sarcoidosis were ruled out on clinical and laboratory grounds, epipharyngeal biopsy and Schirmer’s test. The patient was treated with non-steroid anti-inflammatory drugs for chronic pain syndrome and received prednisolone 3 months after exhibiting cerebral symptoms. Her chronic pain-related symptoms had resolved, whereas other symptoms improved only slightly.

After another 2 years, the patient developed diabetes insipidus and visual impairment. The prolactin level increased slightly, whereas other hormone levels were within the reference ranges for the age. Neuroophthalmological examination revealed bilateral optic atrophy. MRI demonstrated meningeal thickening and contrast enhancement posterior to clivus from the level of posterior clinoid processes, spreading inferiorly to foramen magnum and dens axis, and laterally to sigmoid sinuses, basis of posterior fossa and foramen jugulare. The meningeal thickening progressed at 1-year follow-up, but withoutellar or suprasellar involvement. Radiology and clinical findings led to suspected meningeal sarcoidosis diagnosis.

Biopsy from the dura covering posterior fossa showed diffuse fibrosis, focally with a tendency toward the storiform pattern, a mixed IgG4-related inflammatory, and spread necrotising granulomas surrounded by epithelioid cells and a few multinucleated giant cells. No microbial agents were suspected on the PAS or Ziehl-Neelsen stains.

Extended investigation with laboratory tests for microbial agents (Mycobacterium tuberculosis, Brucella, Bartonella, Treponema pallidum and human immunodeficiency virus) was negative. A repeated high-resolution CT chest was normal and, as previously, cerebral spinal fluid analysis revealed non-specific inflammatory findings. Finally, based on the MRI and dura biopsy findings, the patient was diagnosed with chronic granulomatous pachymeningitis with IgG4-related pathology, whereas meningeal sarcoidosis was also considered in the differential diagnosis but not confirmed.

During the 10-year-follow-up, the patient’s most prominent symptoms have been progressive visual loss, diabetes insipidus, headache and fatigue. Initially, repeated MRI demonstrated continuous slight progression of the dural thickening and contrast enhancement with obliteration of cavum Meckeli, affection of anterior spinal dura to the lower thoracic level (Th 9-11), cavernous sinuses, frontal dura and apex of the right orbital area. However, in the last 5 years, the MRI findings have been stable.

The patient has been treated with moderate to high doses of corticosteroids (betamethasone and prednisolone), with temporary symptom relief but with worsening of her cerebral symptoms at tapering prednisolone to dose under 10 mg day\(^{-1}\). A concomitant high weekly dose of methotrexate (25 mg week\(^{-1}\)) and rituximab treatment (500-1000 mg as one dose given 1 or 2 times year\(^{-1}\)) was without significant improvement. She developed striking side-effects of corticosteroids with cushingoid features, weight gain and blindness as a complication of severe cataract and glaucoma caused by prolonged high-dose corticosteroid therapy. The patient still has prednisolone 20 mg day\(^{-1}\) and azathioprine 150 mg day\(^{-1}\) to control her cerebral symptoms and she is on substitution therapy for diabetes insipidus.

4 | DISCUSSION

In the present study, we reviewed clinical, histopathological and radiological findings in six patients with pituitary dysfunction and
IgG4 features in surgical specimens. We found additional, non-IgG4-related findings in all the patients.

In accordance with the proposal of Leporati et al\textsuperscript{13} and the biopsy-proven cases of IgG4-RH published so far,\textsuperscript{15,16,18-20} an increased number of IgG4\textsuperscript{+} plasma cells with or without fibrosis has been a basis for the diagnosis. In our cohort, all six patients fulfilled the criteria of Leporati et al\textsuperscript{13} and at least two out of the three criteria as defined by Deshpande et al.\textsuperscript{27} Furthermore, the patients fulfilled the histopathological inclusion criteria of IgG4-RD with at least 20 points, according to the new ACR/EULAR classification criteria for IgG4-RD,\textsuperscript{28} comprising rich lymphoplasmacytic infiltration with an increased number of IgG4\textsuperscript{+} cells (range from 30 to > 50 per HPF, ≥ 40\% of all CD138\textsuperscript{+} plasma cells) and fibrosis with at least focal storiform pattern. In one patient, signs of obliterative phlebitis were also present.

The additional morphological changes that are not part of IgG4-RD were identified in an otherwise typical histological landscape of IgG4-RD in all surgical specimens. In two patients, one with a specimen from the pituitary gland (patient 1 with GPA diagnosis) and one with a specimen from the dura (patient 6 with chronic pachymeningitis), we have demonstrated granulomatous changes. Granulomatous hypophysitis may be associated with ruptured Rathke’s cleft cyst, craniopharyngioma, microbial agents and systemic granulomatous disorder, or may represent a late stage of lymphocytic hypophysitis.\textsuperscript{29} One of the previously published cases of the histologically typical IgG4-RH was initially diagnosed as granulomatous hypophysitis.\textsuperscript{21} Nonetheless, Bernreuther et al\textsuperscript{16} have specifically emphasised the absence of a rich infiltration by IgG4\textsuperscript{+} plasma cells in six cases of granulomatous hypophysitis in their cohort. Systemic granulomatous inflammation with the involvement of the pituitary gland in patients with GPA is rare.\textsuperscript{30-32} An increased number of IgG4\textsuperscript{+} plasma cells has been observed in the context of GPA and can, in combination with fibrosis, which is a frequent finding in GPA, represent a pitfall in the diagnosis of IgG4-RH.\textsuperscript{34} Both our patients with granulomatous changes in the pituitary and dura, respectively, were ANCA positive and also had imaging findings in their lungs, suggestive of either ANCA-associated vasculitis or IgG4-related lung disease. Lung biopsies, however, were not performed. These two cases indicate that histopathological features of IgG4-RD may overlap with those seen in ANCA associated vasculitis, as reported in other studies of pituitary and retrobulbar IgG4-RD and ANCA associated vasculitis.\textsuperscript{35,36} Regarding patient 6, meningeal sarcoidosis should also be considered in the differential diagnosis despite normal ACE. We suggest that, if the findings of IgG4-pathology and granulomatous process co-exist in the pathology specimen in a patient, it should then prompt the physician to search for other systemic manifestations. Biopsies from other affected organs could help in these cases for diagnosis and treatment. Both patients with ANCA-associated vasculitis and patients with IgG4-RD, usually respond well to treatment with glucocorticoids and rituximab. However, to induce remission in ANCA-associated vasculitis, more aggressive treatment strategies can be required.\textsuperscript{37}

Furthermore, besides IgG4-related histopathology, three patients in our cohort had evidence of Rathke’s cleft cyst in the surgical specimens and, in one patient, fragments of Rathke’s cleft cyst were suspected. Rathke’s cleft cyst can cause an inflammation of the pituitary gland, especially when ruptured.\textsuperscript{38} The inflammatory reaction surrounding Rathke’s cyst can be associated with xanthomatosus\textsuperscript{39} or lymphocytic\textsuperscript{40} hypophysitis. However, IgG4 histopathological changes accompanying Rathke’s cyst have only recently been suspected.\textsuperscript{41}

The presence of additional pathological features such as epithelioid granulomas and Rathke’s cleft cyst in patients with pituitary dysfunction, in the otherwise typical histological landscape of IgG4-RD in surgical specimens, raises the question of the mechanisms triggering local IgG4 cell proliferation and fibrosis in the sellar region.\textsuperscript{29} Granulomas and a cystic process, frequently corresponding to Rathke’s cyst, followed by inflammatory changes, have also been observed in five and six, respectively, out of 14 patients with inflammatory changes in the pituitary specimens without evidence of IgG4-related pathology. This suggests that granulomas and Rathke’s cyst coexist with IgG4-related histopathology only in a subset of patients with a predisposition to the proliferation of IgG4\textsuperscript{+} plasma cells and fibrosis. These findings can also be supported by a recently reported co-occurrence of IgG4-RH and a craniopharyngioma.\textsuperscript{42} Genetic predisposition and presence of autoantibodies have already been suggested as mechanisms responsible for the development of IgG4-RD.\textsuperscript{43-45}

Clinical features in our patients with IgG4-related pituitary dysfunction are similar to the previously published data concerning IgG4-RH. The preponderance of female patients (2:1) and mean age (55 years; range 42-71 years) are in concordance with the majority of published histologically proven cases (mean age 54 years), although Bernreuther et al\textsuperscript{16} reported a lower mean age (42 years) in a series of 12 cases. However, in general, the IgG4-RD predominantly affects men in their 60s, with the possible exception of those with head and neck involvement, in whom the gender distribution is almost equal.\textsuperscript{5,46}

Diabetes insipidus was present in as many as five of the six patients. An anterior pituitary insufficiency also dominated in our patients, as also frequently reported in the literature.\textsuperscript{15,47} Interestingly, the patient with pachymeningitis had only isolated diabetes insipidus. At the latest follow-up, two patients had panhypopituitarism with full hormone substitution, except for growth hormone (GH) in one patient. However, the GH axis was not evaluated in all of the patients, and the cortisol axis could not be adequately evaluated in the patients treated with high doses of glucocorticoids. None of the patients had recovered from pituitary dysfunction during the follow-up period.

Surgery and, in two patients, anti-inflammatory treatment improved cerebral and visual symptoms, but did not have any effect on changes in hormone replacement therapy. Two of the patients (patients 3 and 6) developed major side effects (iatrogenic Cushing’s syndrome, weight gain, cataract/glaucoma) during longstanding moderate to high doses of systemic glucocorticoids. Early anti-inflammatory and immnosuppressive treatment were introduced only in one patient with co-existing IgG4-related
pathology and GPA (patient 1). This patient is in stable remission under immunosuppressive maintenance therapy with azathioprine after 2 years of regular rituximab treatment. This case also indicates a need for early treatment with anti-rheumatic steroid-sparing drugs and proper maintenance therapy.\(^{25,47}\) Thus, an early histologically confirmed diagnosis and close follow-up by a multidisciplinary team, comprised of an endocrinologist, neurosurgeon, neurologist and neuroradiologist, as well as a rheumatologist, is strongly recommended for the management and follow-up of the patients with IgG4-related pathology of the pituitary gland to prevent long-term glucocorticoid toxicity, unnecessary repeated surgeries, and a relapse of the disease.

In our study, only one patient had slightly increased serum IgG level and possible IgG4-related inflammation in other organs (patient 4), which is consistent with usually isolated pituitary involvement, as in previous reports.\(^{25,47}\) Recently, a study of 27 patients with autoimmune pancreatitis revealed 18.5% of patients with morphological abnormalities in the pituitary; however, only one patient met criteria for hypophysitis.\(^{49}\) Our patient had lung fibrosis diagnosed 2 years before the pituitary dysfunction symptoms and recurrent pancreatitis after IgG4-RH diagnosis; thus, his lung and pancreas manifestations could be associated with systemic IgG4-RD. Although rare, the possibility of a systemic IgG4-RD should be considered in patients with IgG4-RH.

We could not identify any specific MRI features for IgG4-RH. Five patients who underwent an operation for pituitary lesion demonstrated a tumour suggestive pituitary mass on MRI. An intraor suprasellar cyst was detected on MRI in three out of four patients with histological evidence of Rathke’s cleft cyst. Marked fibrosis in all cases may explain the lack of specific MRI features and represents differential diagnostic difficulties versus a neoplastic sellar process. In a recent study,\(^{50}\) the findings in 17 patients with IgG4-RD in different areas of the brain, head and neck were described, where two patients had pituitary lesions. Typical findings were well-defined lesion borders, T2 hypointensity, a homogeneous and gradual enhancement pattern, absence of vascular occlusion or compression, and the presence of bone remodelling without destruction. In our material, T2 hypointensity, suggesting fibrosis, was observed in patient 4 and partially in patient 2. In addition, there was a low enhancement in patient 5, which could also be an indication of fibrosis, although the water content was high.

Interestingly, patient 6 has never had MRI confirmed pathology in the sellar region despite persistent diabetes insipidus during a 10-year follow-up. Her main MRI manifestation has been pachymeningitis, which is one of the typical intracranial manifestations of IgG4-RD.\(^{28}\) This peculiar clinical presentation may suggest initial radiologically undiagnosed pituitary involvement, followed by propagation of the IgG4-process to the meninges. Similar to the IgG4-RH, the pachymeningitis frequently occurs in the absence of the extracranial disease and multiorgan involvement.\(^{67}\) Concomitant pituitary and meningeal involvement in the context of IgG4-RD have previously been reported,\(^{51}\) suggesting an intracranial propagation of the process.

Diagnostic criteria for IgG4-RH are still based on a proposal by Leporati et al\(^{25}\) from 2011 and consider the presence of 10 IgG4\(^+\) plasma cells/HPF as a single diagnostic criterion. Having the number of IgG4\(^+\) cells as the only criterion, without storiform fibrosis or any exclusion criterion, may result in an overdiagnosis of the IgG4-RH. The reported prevalence of IgG4-RH is around 4% in patients with hypopituitarism and/or central diabetes insipidus,\(^{14,27}\) whereas no conclusions regarding the prevalence of the IgG4-RH may be generated from our study. However, the presence of the histological features not typically associated with the IgG4-RD in five out of 12 patients in our cohort supports the speculation that IgG4-RH can be an overdiagnosed condition. The application of the ACR/EULAR classification criteria to our patients would result in the exclusion of at least two patients with granulomatous changes despite showing the typical IgG4-related pathology. Thus, we propose that the recently published ACR/EULAR classification criteria\(^{28}\) should also be considered in patients with IgG4-related pathology findings in the pituitary gland to avoid overdiagnosis. However, it is not clear how the patients with a cystic process (e.g., Rathke’s cleft cyst) would be considered in the light of these classification criteria.\(^{28}\) Even if the presence of additional findings such as granulomas or Rathke’s cyst would exclude the pathological diagnosis of IgG4-RH, the IgG4-related changes should be reported by pathologists because the presence of these features may be associated with atypical clinical and MRI findings and an unexpected response to surgical or pharmacological therapies. Moreover, the presence of IgG4-associated histological features should prompt generalised work-up and the search for systemic manifestations of IgG4-RD.

5 | CONCLUSIONS

The preoperative diagnosis of IgG4-RH is difficult as a result of the lack of specific clinical and imaging features and the frequent absence of systemic manifestations. Additional histopathological lesions not typically associated with IgG4-RD may suggest a possible overlap with other pathological processes or can play a specific role as a potential trigger to arise of the intrasellar and intracranial IgG4-related inflammation and fibrosis. The coexistence of IgG4-related pathology and other lesions such as Rathke’s cyst or granulomata in patients with the pituitary disease may be associated with atypical clinical and MRI presentations and the lack of a response to standard surgical and pharmacological treatment. The current criteria for IgG4-RH are too limited for the correct classification of patients as having isolated IgG4-RH. Therefore, we recommend applying the ACR/EULAR classification criteria for IgG4-RD even to the pituitary gland.

ACKNOWLEDGEMENTS

Figure 1 has been formatted with the valuable assistance by Dr Evelina Sjöstedt. Any grants or fellowships supporting the writing of the paper: Lilian Vasaitis was supported by the Postdoctoral...
Fellowship Program from the Swedish state under the agreement between the Swedish Government and the county councils (ALF) and a grant from ALF supported Olivera Casar-Borota.

CONFLICT OF INTERESTS
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
Lilian Vasaitis: Conceptualisation; Formal analysis; Funding acquisition; Supervision; Visualisation; Writing – original draft; Writing-review & editing. Johan Wikström: Data curation; Formal analysis; Investigation; Methodology; Supervision; Visualisation; Writing – original draft; Writing – review & editing. Sengul Ahlström: Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. Eva Kumlien: Investigation; Methodology; Resources; Supervision; Visualisation; Writing – original draft; Writing – review & editing. Lilian Vasaitis: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Visualisation; Writing – original draft; Writing – review & editing. Britt Edén Engström: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Visualisation; Writing – original draft; Writing – review & editing. Sengul Ahlström: Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. Olof Ahlström: Investigation; Methodology; Writing – original draft. Eva Kumlien: Data curation; Resources; Writing-original draft; Writing-review & editing. Britt Edén Engström: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Visualisation; Writing – original draft; Writing – review & editing. Lilian Vasaitis: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Supervision; Validation; Visualisation; Writing-original draft; Writing – review & editing.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/jne.12942.

ORCID
Lilian Vasaitis https://orcid.org/0000-0001-6715-3704

REFERENCES
43. Ota M, Katsuyama Y, Hamano H, et al. Two critical genes (HLA-DRB1 and ABCF1) in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics*. 2007;59:45-52.