Autoimmune hypophysitis: expanding the differential diagnosis to CTLA-4 blockade

Angelika Gutenberg, Melissa Landek-Salgado, Shey-Cherng Tzou, Isabella Lupi, Abby Geis, Hiroaki Kimura and Patrizio Caturegli†

†Author for correspondence
Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
Tel.: +1 443 287 8911 Fax: +1 410 614 3548 pcat@jhmi.edu

Autoimmune hypophysitis is an increasingly recognized disorder that enters in the differential diagnosis of nonfunctioning pituitary masses. The differential diagnosis of these conditions is challenging because of similar clinical presentations and radiological signs. This review describes the essential features of hypophysitis and the other nonfunctioning pituitary masses. It also emphasizes a recently described feature of hypophysitis: its appearance with unexpectedly high frequency in patients receiving treatments that abrogate the function of cytotoxic T lymphocyte antigen 4.

Keywords : autoimmunity • CTLA-4 blockade • hypophysitis • monoclonal antibodies • MRI • nonfunctioning sellar masses

General features of autoimmune hypophysitis

Autoimmune (lymphocytic) hypophysitis (AH), is a chronic inflammation of the pituitary gland caused or accompanied by pituitary autoimmunity [1,2]. It can be classified etiologically into two groups: primary and secondary hypophysitis.

Primary hypophysitis is, by definition, of unknown etiology. It is diagnosed on clinical and radiological grounds or, when available, by pathological examination. Pathology classifies primary hypophysitis into three forms: lymphocytic, granulomatous and xanthomatous, although some patients have mixed lymphocytic and granulomatous or granulomatous and xanthomatous forms, so that the relationship between these entities remains to be established. Lymphocytic hypophysitis is the most common form and the topic of this review. Granulomatous hypophysitis is characterized by an infiltration of multinucleated giant cells and histiocytes, surrounded by lymphocytes, mainly T cells [3], and plasma cells. Xanthomatous hypophysitis is very rare; it was originally described in 1998 in three women [4], and in eight additional patients thereafter [3,5–8]. It features cystic-like areas of liquefication, infiltrated by lipid-rich foamy histiocytes and lymphocytes.

Secondary hypophysitis is caused by local or systemic processes. Local processes that arise within or around the pituitary gland and are associated with lymphocytic infiltration of the pituitary gland include germinoma [9], ruptured Rathke cleft cyst [10], pituitary adenoma [11], and craniopharyngioma [12]. Systemic processes that involve the pituitary are most commonly associated with a granulomatous reaction and include Wegener granulomatosis [13], sarcoidosis [14], Langerhans cell histiocytosis [15] and, more rarely nowadays, TB [16]. In the last 5 years a new entity has emerged in this group: hypophysitis secondary to the administration of an antibody that blocks cytotoxic T-lymphocyte antigen 4 [17], an entity that will be explored in detail in this review.

Autoimmune hypophysitis was first reported in 1962 in a young woman who died 14 months after delivery of her second child because of severe adrenal insufficiency [18]. Only 12 additional patients, mainly post-mortem, appeared in the literature during the following 20 years. The first two ante-mortem patients diagnosed by CT scan were reported in 1980 [19,20] and the first one diagnosed by MRI in 1988 [21]. The widespread use of MRI and greater awareness of AH in the medical community have significantly increased the number of published AH patients (Figure 1). Many others are diagnosed but not published, and even more patients remain undiagnosed because of varying clinical presentations and courses. Thus, although AH has been traditionally considered a rare disease, it
Autoimmune hypophysitis can affect just the anterior pituitary lobe (adenohypophysitis), just the posterior lobe and the stalk (infundibulo-neruohypophysitis) or both (panhypophysitis). It is unclear whether these conditions represent different diseases or a spectrum of the same disease. The distinction can also be misleading because a biopsy of both the anterior and posterior lobes is only rarely performed, or specified in the published reports.

Autoimmune hypophysitis is approximately three-times more common in females than males (389 female and 138 male; ratio: 2.8:1); especially when it affects preferentially the anterior lobe (273 female and 65 male; ratio: 4.2:1). The disease is most common during the fourth decade of life, with a mean age at presentation of 39 (median 35) years. As is common for such diseases, AH tends to occur together with other autoimmune diseases, most frequently with those affecting the thyroid gland [1].

The diagnosis of AH remains difficult because it mimics the clinical and even radiological features of all other nonsecreting pituitary masses of a reasonable size [23]. The symptoms of AH are mainly neurological and endocrinological. Neurological symptoms stem from compression of the structures surrounding the pituitary gland, and thus include headache (meninges), visual disturbances (optic chiasma) and diplopia (oculomotor nerves). Endocrinological symptoms are due to compression or invasion of the normal anterior pituitary (leading to adrenal insufficiency, hypothyroidism and hypogonadism), posterior pituitary (diabetes insipidus) or pituitary stalk (hyperprolactinemia).

The treatment of AH is, at the moment, only symptomatic. It aims to reduce the size of the pituitary mass and replace the deficient hormones. High-dose glucocorticoids (prednisolone 60 mg daily, tapering the dose every 5 days) are generally recommended as first-line treatment in cases suspected for AH where vision is not endangered by the pituitary mass. Improvement under glucocorticoids, however, is sometimes incomplete, transient or even lacking, especially in cases that have a granulomatous or xanthomatous component [23]. If vision is endangered or symptoms worsen, trans-sphenoidal surgery has to be performed. In addition to reducing the mass size, this procedure also yields pituitary tissue for pathological analysis, which is still considered the gold standard for diagnosing AH. Given the diffuse nature of the pituitary lesion in AH, neurosurgical decompression should not be radical. Follow-up intervals after surgery should be short and include endocrinological and radiological updates as recurrence of AH following trans-sphenoidal surgery is well described [24]. In AH patients with aggressive course that have not responded to the two treatments indicated above (glucocorticoids, and trans-sphenoidal surgery), other approaches have been successfully applied. These include lympholytic drugs other than glucocorticoids, such as azathioprine [25], methotrexate [26,27] or rituximab [28], stereotactic radiotherapy [29] and, more recently, γ-knife surgery [30].

The natural history of AH is variable. Most patients improve after reduction of the pituitary mass (obtained through surgery or glucocorticoid therapy), and either require long-term hormonal replacement therapy (73%) or no medication (17%). Glucocorticoids, when started early during the disease course, can significantly ameliorate the patient’s status and even halt the progression to a chronic phase. The hypopituitarism developing in the early phases of AH can, in fact, occur via two mechanisms: the direct destruction of the endocrine cells induced by the lymphocytic infiltrate, and the compression and impairment of the endocrine cells secondary to the inflammatory edema. The latter mechanism is corrected by glucocorticoid administration. Indeed, a clinical response to glucocorticoids is a good indication that the diagnosis of a nonbiopsied pituitary mass is indeed AH. A few AH patients improve spontaneously without treatment (4%). The remaining patients (6%) die because of an irreversible, late-diagnosed adrenal insufficiency. The most recent patient reported as an autopsy case was published in March 2009 [31], and showed a clinical history not dissimilar from that of the first patient reported in 1962, reminding us that AH can still be a lethal disease if unrecognized.

is probably underestimated [22]. At Johns Hopkins we maintain a database of published patients with primary AH that, as of October 15 2009, includes 522 cases downloadable from our website [201]. Patients have been reported from several countries, but predominantly Japan and the USA (Figure 2). Within these countries, reporting is, as expected, greatest in areas rich in academic centers. Many authors have written about AH, creating a database of published patients with primary AH that, as of October 15 2009. The articles have all been scanned and are now freely downloaded from our website [201]. The top-five publishing centers currently are Federico II University of Naples, Naples, Italy (De Bellis A, 19 articles); Gunma University, Gunma, Japan (Kobayashi I, 13 articles); Kochi Medical School, Kochi, Japan (Hashimoto, K, 12 articles); Johns Hunter Children’s Hospital, New South Wales, Australia (Crock P, ten articles); and Johns Hopkins University, MD, USA (Cateregli P, ten articles).

Autoimmune hypophysitis remains difficult to diagnose because it mimics the clinical and radiological features of all other nonsecreting pituitary masses of a reasonable size [23]. The symptoms of AH are mainly neurological and endocrinological. Neurological symptoms stem from compression of the structures surrounding the pituitary gland, and thus include headache (meninges), visual disturbances (optic chiasma) and diplopia (oculomotor nerves). Endocrinological symptoms are due to compression or invasion of the normal anterior pituitary (leading to adrenal insufficiency, hypothyroidism and hypogonadism), posterior pituitary (diabetes insipidus) or pituitary stalk (hyperprolactinemia).

The treatment of AH is, at the moment, only symptomatic. It aims to reduce the size of the pituitary mass and replace the deficient hormones. High-dose glucocorticoids (prednisolone 60 mg daily, tapering the dose every 5 days) are generally recommended as first-line treatment in cases suspected for AH where vision is not endangered by the pituitary mass. Improvement under glucocorticoids, however, is sometimes incomplete, transient or even lacking, especially in cases that have a granulomatous or xanthomatous component [23]. If vision is endangered or symptoms worsen, trans-sphenoidal surgery has to be performed. In addition to reducing the mass size, this procedure also yields pituitary tissue for pathological analysis, which is still considered the gold standard for diagnosing AH. Given the diffuse nature of the pituitary lesion in AH, neurosurgical decompression should not be radical. Follow-up intervals after surgery should be short and include endocrinological and radiological updates as recurrence of AH following trans-sphenoidal surgery is well described [24]. In AH patients with aggressive course that have not responded to the two treatments indicated above (glucocorticoids, and trans-sphenoidal surgery), other approaches have been successfully applied. These include lympholytic drugs other than glucocorticoids, such as azathioprine [25], methotrexate [26,27] or rituximab [28], stereotactic radiotherapy [29] and, more recently, γ-knife surgery [30].

The natural history of AH is variable. Most patients improve after reduction of the pituitary mass (obtained through surgery or glucocorticoid therapy), and either require long-term hormonal replacement therapy (73%) or no medication (17%). Glucocorticoids, when started early during the disease course, can significantly ameliorate the patient’s status and even halt the progression to a chronic phase. The hypopituitarism developing in the early phases of AH can, in fact, occur via two mechanisms: the direct destruction of the endocrine cells induced by the lymphocytic infiltrate, and the compression and impairment of the endocrine cells secondary to the inflammatory edema. The latter mechanism is corrected by glucocorticoid administration. Indeed, a clinical response to glucocorticoids is a good indication that the diagnosis of a nonbiopsied pituitary mass is indeed AH. A few AH patients improve spontaneously without treatment (4%). The remaining patients (6%) die because of an irreversible, late-diagnosed adrenal insufficiency. The most recent patient reported as an autopsy case was published in March 2009 [31], and showed a clinical history not dissimilar from that of the first patient reported in 1962, reminding us that AH can still be a lethal disease if unrecognized.
Figure 2. Distribution of 522 published patients with primary autoimmune hypophysitis according to the geographic location of the first author. Worldwide, USA and Japanese distributions.
Autoimmune hypophysitis has at least three features that are intellectually challenging and stimulating. First, it shows a striking but unexplained temporal association with pregnancy. Second, it remains one of the few organ-specific autoimmune diseases where the autoantigens have not yet been identified. Lastly, it develops with unexpectedly high frequency in patients receiving treatments that block CTLA-4. This review will focus on the differential diagnosis of AH, emphasizing its expansion to include CTLA-4 blockade.

**Association of CTLA-4 blockade & AH**

It is now well established that the immune system recognizes cancer cells and plays an important role in their control, so much so that humans and animals with a defective immune system are at greater risk of developing cancer [32]. Cancer cells, however, evade such immune surveillance in most patients. Despite enormous efforts and resources being dedicated to the development of immunotherapies, none of them are currently indicated as a standard, first-line anticancer treatment [33]. Cancer cells escape the immune system surveillance using four main types of mechanisms illustrated in Figure 3. The first mechanism, directly relevant to this review, involves the recruitment to the tumor site and draining lymph nodes of suppressor T cells (Tregs), tolerogenic dendritic cells [34], myeloid-derived suppressor cells [35] and tumor-associated macrophages (Figure 3) [36].

Tregs are a subset of CD4 T lymphocytes that suppress the activity of CD8 effector T lymphocytes, CD4 helper T lymphocytes and antigen-presenting cells. Tregs are mainly characterized by the intracellular expression of the forkhead box P3 transcription factor [37]. They also express constitutively CTLA-4, CD25 (the α chain of the IL-2 receptor) and the glucocorticoid-induced TNF receptor; secrete the immunosuppressive cytokines IL-10 and TGF-β; and have minimal levels of effector cytokines (e.g., IFN-γ and TNF-α) and cytotoxic molecules (e.g., granzyme B) [37]. Tregs are beneficial in that they keep autoimmunity in check, but they are also detrimental in tumor immunology because they inhibit the anti-tumor action of effector T cells. Notably, there is a strong inverse correlation between the number of intratumoral Tregs and the extent of tumor necrosis: the higher the number of intratumor Tregs the smaller the capacity of CD8 T cells to induce tumor necrosis (reviewed in [38]).

CTLA-4 (Figure 3, inset) is a regulatory molecule expressed constitutively on the surface of Tregs. It binds to the costimulatory molecule B7 on dendritic cells, sending inhibitory signals that ultimately impair the immune-activating capacities of dendritic cells [39]. CTLA-4 is also expressed on effector T cells but only after T-cell activation; it is initially found in cytosolic vesicles located near the immunologic synapse, and then on the cell surface peaking at 2–3 days after activation [40]. Thus, CTLA-4 acts bidirectionally (on both dendritic cells and effector T cells) to

---

**Figure 3. Mechanisms used by cancer cells to escape recognition by the immune system.** Inset: function of CTLA-4. ARG: Arginine; CSF: Cerebrospinal fluid; CTLA: Cytotoxic T lymphocyte antigen; NOS: Nitric oxidase synthase; PG: Prostaglandin; TCR: T-cell receptor.
ultimately inhibit T-cell function and prevent the development of autoimmunity. Deletion of Ctla-4 in mice leads to aggressive autoimmune reactions characterized by lymphoproliferation and multiorgan failure [41], secondary to defective Treg activity and unopposed effector T-cell activation. Similarly, in humans, polymorphisms in the CTLA-4 gene that decrease its RNA stability and function have been associated with increased susceptibility to Type 1 diabetes mellitus and autoimmune thyroiditis [42].

Considering the inhibitory effects of CTLA-4 on lymphocyte function and the notion that immune responses against cancer cells are usually inhibited, investigators have blocked CTLA-4 with the intent of inducing a general immune stimulation. That is, inhibiting an inhibitor such as CTLA-4 should ultimately result in an overall enhanced immune response, and thus also in an enhanced immune response against cancer cells. Inhibition of CTLA-4 is achieved in patients by the injection of a monoclonal antibody that disrupts the CTLA-4/B7 interaction, ultimately abrogating CTLA-4 function [43]. This treatment regimen, combined or not with vaccination protocols against cancer antigens, is being tested in patients with malignant melanoma, renal cell carcinoma, ovarian cancer, prostate cancer and other solid tumors [44–46].

There are currently two anti-CTLA-4 monoclonal antibodies in Phase I clinical trials: ipilimumab (MDX-010, by Medarex and Bristol Myers Squibb) and tremelimumab (or ticilimumab [CP-675,206] by Pfizer) [47]. The largest experience is with ipilimumab [48]. CTLA-4 blockade is an effective anticancer treatment. It induces, on average, cancer regression in approximately 15% of the patients, although results are variable among trials [44]. CTLA-4 blockade promotes anticancer responses via at least two mechanisms. Blocking CTLA-4 on tumor-specific effector T cells avoids their inhibition, promoting their clonal expansion [49]. Blocking CTLA-4 on Tregs leads to their depletion, thus releasing the brake that Tregs place on effector T cells, both tumor specific and nontumor specific [50]. Several randomized Phase III clinical trials based on CTLA-4 blockade are currently ongoing (listed at [202]).

The expected ‘side effect’ of CTLA-4 blockade, known as immune breakthrough event or immune-related adverse event (IRAE), is the induction of autoimmune diseases. They are reported in up to 43% of patients [51] and have a variable and unpredictable course. In some cases the course is fulminant, such as the development of diffuse colitis with crypt abscess formation 7 days after the first dose of ipilimumab [52]. The most common IRAEs due to anti-CTLA-4 therapy are inflammatory bowel disease (colitis), hypophysitis, skin reactions and hepatitis, although numerous others are described [17].

Autoimmune hypophysitis secondary to CTLA-4 blockade was first reported in eight out of 163 (5%) melanoma patients published by the National Cancer Institute [53,54], and its appearance was associated with a favorable response in five out of the eight patients. AH incidence ranges from a minimum of 1.8% [55] to a maximum of 17% [56], both in trials of patients with metastatic melanoma. The clinical description of AH manifestations in these case series is limited, but more recently four individual publications have described a total of seven patients [17,57–59]. The clinical presentation is similar and indistinguishable from that of patients with classic AH: patients complain of headache and symptoms of anterior pituitary hormone deficiencies. Furthermore, the MRI is similar, showing a diffuse enlargement of the pituitary gland [57]. The diagnostic hint for this form of secondary AH is the underlying cancer and the use of CTLA-4-blocking antibodies. AH symptoms usually improve upon discontinuation of CTLA-4 blockade, and with the use of immunosuppressive doses of glucocorticoids [58]. The endocrine defects are long-lasting and require a prolonged follow-up, so much so that specific algorithms should be included in anti-CTLA-4 therapy protocols [17].

It remains unknown why AH, a disease traditionally considered to be very rare, appears preferentially in the settings of CTLA-4 blockade. Efforts aimed at unraveling this association can greatly

Table 1. Classification of sellar (intrasellar and parasellar) masses.

<table>
<thead>
<tr>
<th>Disease</th>
<th>% of sellar masses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone-secreting pituitary adenomas</strong></td>
<td>56</td>
</tr>
<tr>
<td>PRL-secreting adenoma</td>
<td>42</td>
</tr>
<tr>
<td>ACTH-secreting adenoma</td>
<td>8</td>
</tr>
<tr>
<td>GH-secreting adenoma</td>
<td>5</td>
</tr>
<tr>
<td>TSH-secreting adenoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nonfunctioning sellar masses</strong></td>
<td>44</td>
</tr>
<tr>
<td>Benign tumors</td>
<td></td>
</tr>
<tr>
<td>Nonfunctioning pituitary adenoma</td>
<td>32.0</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1.20</td>
</tr>
<tr>
<td>Meningioma</td>
<td>0.96</td>
</tr>
<tr>
<td>Developmental lesions</td>
<td></td>
</tr>
<tr>
<td>Rathke’s cleft cyst</td>
<td>3.96</td>
</tr>
<tr>
<td>Cranioopharyngioma</td>
<td>1.92</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>0.48</td>
</tr>
<tr>
<td>Dermoid and epidermoid cysts</td>
<td>0.36</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td></td>
</tr>
<tr>
<td>Metastasis (mainly from breast and lung cancer)</td>
<td>1.20</td>
</tr>
<tr>
<td>Germinoma</td>
<td>0.24</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.12</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>0.15</td>
</tr>
<tr>
<td>Autoimmune and inflammatory lesions</td>
<td></td>
</tr>
<tr>
<td>Hypophysitis (lymphocytic and granulomatous)</td>
<td>0.84</td>
</tr>
<tr>
<td>Sphenoidal sinus mucocele</td>
<td>0.12</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0.12</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>0.06</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Infectious lesions</strong></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>0.12</td>
</tr>
<tr>
<td>Pituitary abscess</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Vascular lesions</strong></td>
<td></td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>0.06</td>
</tr>
<tr>
<td>Intrasellar aneurysm</td>
<td>0.06</td>
</tr>
</tbody>
</table>
| ACTH: Adrenocorticotropic hormone; GH: Growth hormone; TSH: Thyroid-stimulating hormone. Data derived and simplified from [60,72].
advance our understanding of AH pathogenesis and autoimmunity. At the very least, the CTLA-4/AH association is contributing to an increased awareness of AH in the medical community.

Differential diagnosis of nonfunctioning sellar masses
Masses that arise within (intrasellar) or around (parasellar) the sella turcica, so-called sellar masses, can be of neoplastic, developmental, inflammatory, infectious or vascular origin (Table 1) [60,61]. The most common sellar mass is the hormone-secreting pituitary adenoma, representing more than half (56%) of all sellar masses. Its diagnosis is greatly facilitated by the signs and symptoms that arise as a consequence of the hormonal hypersecretion.

Nonfunctioning sellar masses represent a heterogenous group of approximately 20 diseases (Table 1), among which the nonfunctioning pituitary adenoma predominates.

All nonfunctioning sellar masses, despite their diverse etiology, present very similarly but require quite diverse treatments. For example, surgery is indicated for a nonfunctioning pituitary adenoma that impinges upon the optic chiasma causing loss of vision, radiotherapy for a germinoma and glucocorticoids for AH. The presentation is characterized by neurologic and/or hypopituitary symptoms caused by the mass effect. Neurologic symptoms result from compression of the structures surrounding the pituitary: headache (meninges); visual field and acuity defects (optic chiasm); and diplopia (oculomotor nerves). Hypopituitarism results from compression of the normal anterior pituitary, and more rarely, the posterior pituitary (causing diabetes insipidus) or the stalk (causing hyperprolactinemia).

The differential diagnosis of nonfunctioning sellar masses should be based on a multidisciplinary approach and, in an ideal setting, it should be obtained before trans-sphenoidal surgery. In the following section we will discuss the clinical and radiological features that can be used to distinguish AH from the other nonfunctioning sellar masses before surgery. This distinction is crucial for patient care because AH can often be managed with lympholytic medications alone whereas many of the other sellar masses require surgical resection [62].

Autoimmune hypophysitis
Autoimmune hypophysitis has a well-established autoimmune pathogenesis. AH is, in fact, reproducible in mice by immunization with pituitary proteins [63], has the pathological features typical of autoimmune diseases (formation of tertiary lymphoid follicles within the target organ), responds to immunosuppressive therapies (such as glucocorticoids), occurs in the same patient with other diseases of proven autoimmune nature and is accompanied by pituitary antibodies.

For AH, however, the main criteria used to establish a diagnosis of autoimmune disease (unique clinical features, presence of specific autoantibodies and pathological findings) are not easily applicable. In fact, the clinical features of AH are often indistinguishable from those of other nonfunctioning masses arising in the sella turcica; the pituitary antibodies as currently measured are not specific (covered in the next section); and to biopsy the pituitary gland requires an expensive and invasive surgical procedure.

It is, therefore, not surprising that many AH patients are misdiagnosed and undergo trans-sphenoidal surgery for a presumptive diagnosis of nonfunctioning pituitary adenoma [26].

Autoimmune hypophysitis should be suspected when the neurologic and/or hypopituitary symptoms described above appear in relation with pregnancy or post-partum, especially if the woman suffers from additional autoimmune diseases, such as thyroiditis, Addison disease, Sjögren syndrome and Type 1 diabetes mellitus. Lack of symptoms, that is presentation of the mass as incidentaloma, is very rare for AH [64]. It has been proposed that the degree of hypopituitarism is disproportionate to the size of the pituitary mass [65], although the criterion has not been formally tested on a large number of cases and controls. Similarly, it has been proposed that the order in which anterior pituitary hormones are lost in AH is different from that observed in pituitary adenomas where gonadotropins and growth hormone are the first to be impaired [66]. In AH, the hypopituitarism mainly involves the adrenal and thyroid axis, although it is important to emphasize that pituitary hormones were not systematically measured in all reported AH patients, thus ascertainment bias is possible. Overall, the measurement of anterior pituitary hormones is useful and needed to establish a baseline reference for future treatments, but does not help substantially in distinguishing AH from the other nonfunctioning pituitary masses.

MRI of the sella turcica is currently the best diagnostic tool, closely reflecting the pathological changes of a pituitary gland targeted by the autoimmune attack. We have recently published a study that systematically analyzed the MRI features of AH in comparison with those of nonfunctioning pituitary adenomas [67]. In keeping with the inflammatory changes and hypervascularity seen during the florid phase of hypophysitis, AH appears on MRI as a symmetrical enlargement of the pituitary gland, homogeneous on T1- and T2-weighted images, both before and after the intense gadolinium enhancement [67,68]. Two additional MRI features indicative of AH are the loss of the normal bright appearance of the posterior pituitary [69] and the thickening of the stalk, probably indicating an autoimmune involvement of the neurohypophysis, even if the patient has not yet developed clinical diabetes insipidus.

Nonfunctioning pituitary adenoma
Nonfunctioning pituitary adenomas lack clinical or biochemical manifestations of hormonal excess. They derive most commonly from the gonadotrophs [70], although each pituitary cell type can give rise to tumors that remain clinically silent [71,72]. They present with headache (48%), visual field and acuity defects (48%) and hypogonadism (55%) [73]. Modest hyperprolactinemia secondary to hypothalamic–pituitary stalk compression is common (47%) [73], whereas diabetes insipidus is extremely rare (<1%) [74]. The duration of symptoms before diagnosis is long, 23 ± 35 months, and it is not unusual even for large tumors to remain asymptomatic and be discovered incidentally after a cranial imaging study is performed for unrelated reasons [75]. Trans-sphenoidal surgery and removal of the adenoma is mandatory if vision is endangered [75].

Nonfunctioning pituitary adenomas are usually macroadenomas when they are symptomatic (diameter >10 mm) and often extend upwards into the suprasellar cistern, or even the third
ventricle and the foramen of Monro. This upward extension provides the tumor a typical snowman or figure-of-eight appearance [76]. Their MRI appearance is clearly dishomogenous, particularly on fast T2-weighted images where disseminated areas of signal hyperintensity reflecting cystic or necrotic portions are seen [76]. After gadolinium injection, the adenomatous tissue usually enhances slightly in comparison to the cavernous sinus or normal pituitary tissue. Strong enhancement is to be expected only in the presence of secondary inflammatory changes, which are found in approximately 3% of pituitary adenomas [77]. In adenomas, the stalk is often deviated laterally, and the normal posterior pituitary bright spot is almost invariably conserved [67].

**Craniopharyngioma**

Craniopharyngiomas account for approximately 2% of all sellar masses (Table 1) [78]. They are thought to arise from epithelial remnants of the craniopharyngeal duct or the Rathke pouch (adamentinomatous type) or from metaplasia of squamous epithelial cell remnants of the part of the stomadeum that form the buccal mucosa (squamous papillary type) [79,80]. The age at presentation follows a bimodal distribution, with a first peak between 5 and 14 years of age and a second between 65 and 74 years [79]. Craniopharyngiomas are often diagnosed late, sometimes years after the initial symptom appearance. The clinical picture at diagnosis is dominated by headache (62%), visual impairment (67–75%) and various degrees of hypopituitarism (52–87%) [81]. Hyperprolactinemia is found in approximately a third of patients [82]. Characteristic of craniopharyngiomas is the presence of psychiatric deficits, loss of short-term memory and personality changes, which are described in approximately a third of the patients [80]. Currently, surgical excision followed by external-beam irradiation is the main treatment option for residual tumor [82].

Craniopharyngiomas appear as large masses (>20 mm in diameter) in part cystic and in part solid and calcified, located in the suprasellar (75%), supra- and intra-sellar (20%) or intrasellar (5%) regions [83]. Tumoral calcification, which may be best appreciated on CT scan, is particularly common and is seen in 70–90% of childhood craniopharyngiomas and 40–60% of adult tumors [26]. Postcontrast MRI shows a homogeneous gadolinium uptake in the solid part of approximately 60% of craniopharyngioma [78].

**Rathke cleft cyst**

Rathke cleft cysts are cystic sellar and suprasellar lesions. They probably arise from the incomplete obliteration of the Rathke pouch, which develops as a rostral outpouching of the primitive oral cavity during the third or fourth week of embryogenesis and are characterized lined by a single layer of ciliated cuboidal or columnar epithelium with goblet cells. Rathke cleft cysts are twice as common in women than men and usually occur between 30 and 60 years of age [84]. They present with headache (65%), hypopituitarism (39–81%) and visual loss caused by compression of the optic chiasm (38%). Hyperprolactinemia is found in 39% of the patients and diabetes insipidus in 9% [81]. Treatment of Rathke cleft cyst is by trans-sphenoidal surgery [85].

Rathke cleft cysts are smoothly marginated and vary in size from a few millimeters to 10–20 mm. They can be completely intrasellar (40%), or have some suprasellar extension (60%), whereas completely suprasellar cysts are rare [86]. Rathke cleft cysts vary widely in their radiological appearance. Cysts with low protein content are isointense with cerebrospinal fluid on all sequences, but become hyperintense on T1-weighted images as the protein content increases. On T2-weighted images, these cysts are hyperintense in 70% of cases and iso- or hypo-intense in the remaining 30% [86]. A small nonenhancing intracystic nodule is considered a virtually pathognomonic sign of Rathke cleft cyst [78]. These nodules show high signal intensity on T1-weighted images and low signal intensity on T2-weighted images, and lack enhancement, although an enhancing rim of displaced and compressed pituitary gland is present in approximately half of the cases [86]. Calcification is a rarity in Rathke cleft cysts [86].

**Arachnoid cyst**

Arachnoid cysts arise most commonly (40–50%) in the supratentorial compartment, and rarely (9–15%) in the sellar region [87]. They can be congenital or acquired. Sellar arachnoid cysts are attributed to herniation of the arachnoid membrane through an incompetent diaphragma [88]. The mean age at presentation is 45 years (range: 16–80 years) and the time from symptom appearance to diagnosis can vary from 2 weeks to 5 years [89]. Main symptoms include headache (41%) and visual disturbances (55%), whereas hypopituitarism, usually involving the gonadotropic axis, is less common [90]. Hyperprolactinemia is found in 21% and diabetes insipidus in less than 2% of cases [90]. Symptomatic arachnoid cysts are resected via the trans-sphenoidal route.

Arachnoid cysts appear ovoid, smoothly marginated and extending to the suprasellar region [89]. Their signal intensity is the same as that of the cerebrospinal fluid in all sequences, although hemorrhage, high protein content or lack of flow within the cyst may complicate the MRI appearance [86]. Arachnoid cysts show a hypodense signal on T1-weighted sequences and a high signal on T2-weighted images. There is no enhancement of any part of the lesion after contrast agent administration. The normal anterior pituitary can often be recognized only on sagittal planes, and the pituitary stalk is sometimes deviated [89].

**Epidermoid cyst**

Epidermoid cysts arise from ectodermal inclusion during neural tube closure in the third to fifth week of embryogenesis [91]. Acquired epidermoid cysts may develop as a result of trauma but are uncommon in the brain [92]. Epidermoid cysts are present at birth but, because of their slow growth rate, typically remain silent until the second to fourth decade of life [93]. They can occur in numerous locations throughout the brain, including the sellar region, although they are predominantly found in the cerebello–pontine angle cistern. Thus, their clinical presentation varies according to their location. Surgical removal is preferably performed via the trans-sphenoidal route [94].
Most epidermoid cysts are isointense or slightly hyperintense to the cerebrospinal fluid on both T1- and T2-weighted images and typically do not enhance, although some minimal rim enhancement occurs in approximately 25% of cases. Rare ‘white epidermoids’ have high protein content and show high signal intensity on T1- and low signal intensity on T2-weighted images [86].

Meningioma

Meningiomas are three times more common in women than men and peak in incidence during the sixth decade of life [40]. They can originate from any dural surface, including the tuberculum sellae, olfactory groove, sphenoid wing, diaphragma sellae and sella turcica [95]. Purely intrasellar meningiomas are rare [96]. A meningioma originating from the inner surface of the diaphragma sellae grows into the pituitary fossa, mimicking closely a non-functioning pituitary adenoma [96]. Meningiomas originating from the outer layer, by contrast, extend mainly to the supra- and parasellar regions [96]. Patients with tuberculum sellae meningiomas often present with severe visual disturbance, and frontal and orbital headaches (5–20%), but not hypopituitarism; mild-to-moderate hyperprolactinemia may be found at presentation in as many as 50% of patients [97] and the mean duration of symptoms before surgery is approximately 2 years [98]. Sellar meningiomas are known to increase in size and become symptomatic during menses or pregnancy [99]. Progesterone receptor positivity is a risk factor for meningiomas and is found in 81% of female patients versus 40% of male patients [100]. For surgical resection the frontotemporal and petroclival approach is advocated [98,101]. Postoperative residual and/or recurrent tumor, especially within the cavernous sinus, is best controlled by γ-knife radiosurgery [102].

Intrasellar meningiomas typically appear as masses that are hypointense to isointense with respect to the gray matter on both T1- and T2-weighted sequences [103]. They enhance markedly after gadolinium administration in a homogeneous fashion in more than 90% of the cases [103]. Intrasellar meningiomas are commonly associated with sellar enlargement and rarely with an enhancing dural tail [96]. The single most useful finding in differentiating intrasellar meningiomas from AH and pituitary adenomas is to identify the pituitary gland as separate from the mass [95]. Visualization of a cerebrospinal fluid cleft between the tumor mass and the gland, although uncommon, is indicative of meningioma [103]. Hyperostosis of the sellar floor or adjacent bony structures also favors a diagnosis of meningioma, a feature present in approximately a third of the cases [103].

Chordoma

Chordomas arise from embryonic remnants of the primitive notochord and are found entrapped within bone in midline locations, such as the clivus, parasellar region and craniocervical junction (45% of the cases), or the sacrococcygeal region (55%) [104,105]. Intracranial chordomas are more common in females and the young (<26 years of age) [106]. They typically infiltrate and destroy the bone, causing symptoms that vary according to their location. The most common initial complaints are headache, usually reported in occipital or retro-orbital locations, and diplopia, usually caused by palsy of the abducent nerve [109]. Hypopituitarism is rare, although mild dysfunction and hyperprolactinemia have been reported [60]. Trans-sphenoidal surgery followed by radiotherapy is the generally accepted treatment [107].

Intracranial chordomas appear on high-resolution CT as a centrally located, well-circumscribed, soft-tissue mass that arises from the clivus and is associated with extensive lytic bone destruction [60]. Intratumoral calcifications are common but considered to represent inclusions from bone destruction rather than dystrophic calcifications within the tumor itself [108]. MRI is the procedure of choice for detecting a clival chordoma and determining the extent of the tumor and involvement of adjacent structures. Chordomas are iso- to hypo-intense to gray matter on T1-weighted images [108], and have a high signal intensity on T2-weighted images, a finding probably reflecting the high fluid content of vacuolated cellular components [108]. Most intracranial chordomas enhance moderately to markedly after gadolinium administration, with a pattern sometimes referred to as ‘honeycomb’ [109]. Use of the fat suppression technique allows the differentiation of enhanced tumor margins from adjacent bright fatty bone marrow, and better demarcation of intracaval chordomas [110].

Pituitary metastasis

Metastases to the pituitary gland via hematogenous spread typically localize in the posterior pituitary, and thus present as diabetes insipidus [111], considering that the posterior pituitary receives blood directly from the systemic circulation whereas the anterior pituitary is served by the portal system. Metastasis can also occur via meningeal spread through the suprasellar cistern, via the portal circulation from a hypothalamo–hypophyseal or infundibular metastasis, and via extension from a juxtasellar and skull base metastasis. Pituitary metastases are most commonly caused by breast and lung cancer, and are usually found in elderly patients during the sixth or seventh decade of life [112]. Pituitary symptoms are rare because pituitary metastases tend to occur in end-stage cancer patients. Following diabetes insipidus, which is present in approximately 50% of the patients, symptoms include hypopituitarism (25%), bilateral hemianopsia (25%) and headaches (15%); hyperprolactinemia is rare (6% of pituitary metastases) [112].

On MRI, pituitary metastases appear as sellar or suprasellar masses, sometimes with a dumb-bell shape, which are often iso- or hypo-intense to the gray matter on T1-weighted images, and of increased T2 signal [60,95,112]. Masses enhance after gadolinium administration, with a homogeneous, heterogeneous or rim pattern [95]. Thickening of the stalk (21%), erosion of the sellar bone (15%), invasion of the cavernous and sphenoidal sinuses (10%) and loss of the posterior pituitary bright spot (9%) are also described [95,112].

Germ cell tumor

Germ cell tumors of the brain (intracranial germ cell tumors) occur mainly in prepubertal children [113]. Intracranial germ cell tumors include germinomas (65%), of which 85% are considered ‘pure’ germinomas and 15% are germinomas with syncytiotrophoblast giant cells [114], teratomas (18%), embryonal carcinomas (5%),
endodermal sinus tumors (7%) and choriocarcinomas (5%) [15]. Germinomas primarily involving the sellar region are rare and have a predilection for females [116]. They present with diabetes insipids (60–90%), hypopituitarism (75–90%) and visual field defects [117–119]. Hyperprolactinemia, deficiency of growth hormone (GH), adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) are reported in 50, 41.7, 16.7 and 8.3% of the patients, respectively [120]. Sellar germinomas can be difficult to differentiate from AH, even after examination of the pituitary biopsy, since they can show a diffuse lymphocytic infiltration of the pituitary gland similar to that typically seen in AH and are mostly negative for human chorionic gonadotropin (β-hCG), both in the serum and cerebrospinal fluid [114,121,122]. β-hCG, a glycoprotein produced by placental trophoblastic cells, is elevated in choriocarcinomas and in the minority of germinomas that contain syncytiotrophoblast giant cells [114,123]. β-hCG-secreting germinomas are thought to be more aggressive than nonsecreting germinomas, but this notion is controversial [114,123]. We have recently described a girl with intrasellar germinoma initially misdiagnosed as AH [9], and found in the literature eight similar cases reported during the last decade [124–131]. The therapy of choice is irradiation after a confirmatory biopsy is performed [121].

Loss of the normal posterior pituitary bright spot on T1-weighted images is one of the earliest signs in sellar germinomas [95,118], followed by swelling of the stalk and subsequent mass formation, which may displace the enhancing pituitary gland anteriorly [99]. Sellar/suprasellar germ cell tumors have a nonspecific image. They are isointense to cerebral cortex on T1-weighted images (~70%) and enhance solidly. Variable intensities are seen on T2-weighted images [118]. Intratumoral cysts are revealed by MRI in approximately half of the cases [118]. Calcifications may be seen in bigger tumors [95]. Teratomas show a mixed signal intensity with fat and calcifications [60].

**Pituitary lymphoma**

Lymphomas may arise in the CNS directly or through spread from other sites during the natural history of the disease, which is usually associated with progressive widespread systemic disease. Primary CNS lymphoma is defined as a lymphoma limited to the cranio-spinal axis without evidence of systemic disease [132,133]. It represents up to 2% of all primary CNS malignancies and is practically always of the non-Hodgkin type, with the majority being B-cell lymphoma [134]. Pituitary lymphomas are exceedingly rare and are more common in males during the sixth decade of life [135]. Headache is the most common presenting symptom, and results from erosion of the bony sella turcica or stretching of the diaphragma sellae. Like any other nonfunctioning sellar mass, pituitary lymphomas may also present with symptoms of hypopituitarism, which often follows a characteristic sequence characterized by gonadotropin, GH, TSH and, finally, ACTH deficiency [133]. Hypopituitarism, visual field defects, diabetes insipidus and hyperprolactinemia are present at the time of diagnosis in 50, 50, 40 and 20% of the patients, respectively [133]. Cranial nerve involvement owing to lateral extension of the pituitary lymphoma into the cavernous sinus has also been reported [133]. Interestingly, AH has been proposed as a risk factor for subsequent development of pituitary lymphoma [135]. Treatment for this rare malignancy consists of whole-brain radiotherapy [136], combined with systemic chemotherapy and intracranial methotrexate [137].

Sellar lymphomas appear on MRI specifically as homogeneously or heterogeneously enhancing sellar masses, that are is- to hypo-intense relative to gray matter on T2-weighted images [95]. Their appearance, however, varies according to whether the patient has normal or suppressed immunity [95]. In patients with a normal immune system, CNS lymphoma appears as a solitary mass with intermediate-to-low signal intensity relative to gray matter on both T1- and T2-weighted sequences; enhancement with gadolinium is seen in nearly all cases and is homogenous in approximately three quarters of cases [95,134]. The relative lack of T2 prolongation in CNS lymphoma is generally attributed to dense cellularity and a high nucleous-to-cytoplasm ratio, a feature that may be helpful in distinguishing lymphomas from other CNS tumors. This feature, however, has low sensitivity, being present in just over 50% of cases [134]. Calcification and hemorrhage in CNS lymphoma are rare [60,95].

**Sarcoidosis**

Sarcoidosis is a systemic disorder of unknown etiology, characterized histologically by the presence of noncaseating epithelioid granulomas. It is more common in African–American females during the fourth decade of life, where the annual incidence is 107 cases per 100,000 persons [138]. Sarcoidosis of the CNS is evident clinically in approximately 5% of patients [139,140] and at autopsy in approximately 20% [141]. The most common CNS sites of disease activity are the basal meninges and hypothalamus, followed by pituitary stalk and pituitary gland [141,142]. Owing to the hypothalamic involvement, diabetes insipidus is the most common presenting symptom [143], accompanied by other signs of hypothalamic dysfunction, such as impaired thirst, temperature, sleep or weight regulation. Hypopituitarism is rare, a consequence of defective hypothalamic releasing factors [144], and mainly involving the gonadotropin axis [145,146]. Headache (16%), visual dysfunction (10%), diplopia (8–12%) and hyperprolactinaemia (3–32%) are also rare in CNS sarcoidosis. Therapy consists of immunosuppressive agents (e.g., cyclophosphamide, azathioprine or methotrexate) and should be initiated with corticosteroids [147,148].

On MRI, the meningeal, intraparenchymal or sellar lesions of sarcoidosis appear isointense on T1-weighted images and variable on T2-weighted images [60]. These lesions enhance after contrast administration [139], typically accompanied by leptomeningeal enhancement. The pituitary stalk is thickened and enhanced in approximately 50% of patients [145,149], with loss of the normal posterior pituitary bright spot [143,145]. Very rarely, pituitary sarcoidosis shows a cystic appearance [150,151].

**Wegener granulomatosis**

Wegener granulomatosis is a vasculitis of small and medium-sized vessels associated with the presence of antineutrophil cytoplasmic antibodies [152]. It favors Caucasians (90% of patients) [153], equally in males and females [154], and has a mean age at
Table 2. Key clinical and radiological features of nonfunctioning pituitary masses.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>M:F ratio</th>
<th>Mean age (years)</th>
<th>Headache (%)</th>
<th>Visual compromise (%)</th>
<th>DI (%)</th>
<th>Anterior pituitary dysfunction</th>
<th>Cranial nerve palsy (%)</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hypophysitis</td>
<td>1:3</td>
<td>32</td>
<td>53</td>
<td>43</td>
<td>50</td>
<td>ACTH (57%), FSH/LH (52%), TSH (49%), GH (38%), hyperprolactinemia (23%)</td>
<td>3–16</td>
<td>Association with pregnancy</td>
</tr>
<tr>
<td>Nonfunctioning pituitary adenoma</td>
<td>1:1</td>
<td>50</td>
<td>48-68</td>
<td>42</td>
<td>&lt;2</td>
<td>FSH/LH (43%), GH (36%), hyperprolactinemia (28%), ACTH (26%), TSH (24.5%)</td>
<td>7</td>
<td>N/A</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>1:1</td>
<td>5–14 and 65–74</td>
<td>62</td>
<td>67–75</td>
<td>6–9</td>
<td>ACTH (32–50%) FSH/LH (59%), GH (39%), TSH (39%), hyperprolactinemia (32%)</td>
<td>Rare</td>
<td>Psychiatric deficits in 33%</td>
</tr>
<tr>
<td>Rathke cleft cyst</td>
<td>1:2</td>
<td>30–60</td>
<td>65</td>
<td>38</td>
<td>9</td>
<td>ACTH (57%), GH (35%), FSH/LH (53%), TSH (35%), hyperprolactinemia (39%)</td>
<td>Rare</td>
<td>N/A</td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td>1:1</td>
<td>20–40</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>Rare</td>
<td>&gt;50% (no preferred axes)</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Sella arachnoid cyst</td>
<td>1:1</td>
<td>45</td>
<td>41</td>
<td>55</td>
<td>&lt;2</td>
<td>FSH/LH (43%), GH (38%), ACTH (36%), hyperprolactinemia (21%), TSH (&lt;7%),</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Sellar meningioma</td>
<td>1:3</td>
<td>62</td>
<td>5-20</td>
<td>&gt;50</td>
<td>Rare</td>
<td>Hyperprolactinemia &gt;50%, other axes rare</td>
<td>Yes</td>
<td>Progression during pregnancy</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1:2</td>
<td>&lt;26</td>
<td>Usual</td>
<td>Rare</td>
<td>Rare</td>
<td>Unusual</td>
<td>30</td>
<td>N/A</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>1:2</td>
<td>Prepubertal age</td>
<td>Usual</td>
<td>Usual</td>
<td>60–90</td>
<td>Hyperprolactinemia (50%), GH (42%), ACTH (17%), TSH (8%)</td>
<td>Rare</td>
<td>N/A</td>
</tr>
<tr>
<td>Pituitary lymphoma</td>
<td>2:1</td>
<td>Immunocompromised: 30–40; immunocompetent: 60–70</td>
<td>75</td>
<td>50</td>
<td>40</td>
<td>FSH/LH &gt; GH &gt; TSH &gt; ACTH</td>
<td>40</td>
<td>N/A</td>
</tr>
<tr>
<td>Pituitary metastases</td>
<td>1:1</td>
<td>60–70</td>
<td>15</td>
<td>25</td>
<td>45</td>
<td>Partial or global deficiency of anterior lobe in 25%, hyperprolactinemia (6%)</td>
<td>Rare</td>
<td>N/A</td>
</tr>
<tr>
<td>Pituitary tuberculosis</td>
<td>1:2</td>
<td>36.7</td>
<td>91</td>
<td>46</td>
<td>11</td>
<td>Deficiency in 77% without preferential involvement, hyperprolactinemia (23%)</td>
<td>23.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1:2</td>
<td>33.7</td>
<td>16</td>
<td>10</td>
<td>33</td>
<td>Hyperprolactinemia (3–32%), anterior pituitary dysfunction is rare, but FSH/LH mostly affected</td>
<td>8–12</td>
<td>Africans have a threefold increased risk</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>1:1</td>
<td>48</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>Hyperprolactinemia (42%), TSH (42%), FSH/LH (33%), ACTH (17%), GH (17%)</td>
<td>Rare</td>
<td>&gt;90% are Caucasian</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>3:1</td>
<td>35, but 70% under age of 17</td>
<td>Yes</td>
<td>Rare</td>
<td>&gt;90</td>
<td>GH (40–67%), FSH/LH (58%), ACTH (42%), TSH (42%)</td>
<td>Rare</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ACTH: Adrenocorticotropic hormone; DI: Diabetes insipidus; FSH: Follicle-stimulating hormone; GH: Growth hormone; LH: Luteinizing hormone; N/A: Not applicable; TSH: Thyrotropin.
diagnosis of 48 years [155]. The major targets of disease activity are the upper respiratory tract, lungs and kidneys [156]. The PNS is frequently affected, with symmetrical sensory–motor polyneuropathy or mononeuropathy multiplex [154]. CNS involvement is less common and caused by three different mechanisms [157]: direct intracranial extension of the granulomatous process from the sinuses, orbits or mastoid air cells; vasculitis of the cerebral vessels with subsequent ischemic and/or hemorrhagic infarctions; or formation of granulomas directly within the brain parenchyma, remote from the primary disease site.

The pituitary gland is rarely a target of Wegener granulomatosis [158], most often described as thickening of the gland and stalk [155,158–160]. The lesions are typically granulomatous on pathological examination, but pure lymphocytic infiltration of the pituitary gland has been described [23]. Diabetes insipidus is present in all patients affected by Wegener granulomatosis of the pituitary gland [161]. Hypopituitarism is characterized by hypothyroidism (42%), hypogonadism (33%) and GH and ACTH deficiencies (17%) [161]. Hyperprolactinemia is seen in 42% of cases. Visual disturbances [158], ophthalmoplegia [162] or meningitis [163] are rare. Currently, a regimen consisting of daily cyclophosphamide and corticosteroids, which induces complete remission in the majority of patients, is considered standard therapy [164].

The MRI findings of Wegener granulomatosis of the CNS vary widely, reflecting the three mechanisms of CNS involvement highlighted above. The most common findings are thickening and enhancement of the meninges (65%), cerebral infarctions owing to vasculitis (24%), pituitary enlargement (12%), and supra- or infra-tentorial granuloma (<1%) [155]. The pituitary mass most commonly extends to the suprasellar region, although purely intrasellar masses are described [160]. The mass is hypointense on T1- and hyperintense on T2-weighted-images [155,159] and enhances markedly after gadolinium in a homogeneous [155] or heterogeneous fashion depending on the presence of infarction and hemorrhage [159]. Cystic sellar masses that do not enhance with gadolinium are also described [165]. Contrary to what one would predict based on the presence of diabetes insipidus, thickening of the pituitary stalk and loss of the normal posterior bright spot are rarely noticed [159].

Langerhans cell histiocytosis

Langerhans cell histiocytosis is the pathological infiltration of several organs by Langerhans cells [166]. It is most common in children and young adults, so that approximately 70% of the cases occur before 17 years of age. The point prevalence per 100,000 individuals is 0.27 for males and 0.07 for females [167]. The disease most commonly involves bone, skin, lungs, liver, lymph nodes and the hypothalamo–pituitary axis [168]. Diabetes insipidus is the most common endocrine abnormality (~90%) [169], followed by GH deficiency [170]. Hypothyroidism is also common, and can be both secondary to pituitary infiltration [171] or primary because of thyroid infiltration [172]. ACTH deficiency usually occurs in the context of panhypopituitarism but isolated ACTH deficiency is also described [171]. In a study of 12 adult patients with histologically proven Langerhans cell histiocytosis and diabetes insipidus, Kaltzas et al. found deficiency of GH, follicle stimulating hormone, luteinizing hormone, TSH and ACTH in 67, 58, 42 and 42% of the patients, respectively [15]. Hyperprolactinemia is rare [15]. Systemic chemotherapy appears to be of little benefit in controlling the progression of the disease over the long term, although focal radiotherapy may halt local disease progression in terms of mass effects [15].

A pituitary mass caused by Langerhans cell histiocytosis is hypointense on T1-weighted images and hyperintense on T2-weighted images, and enhances brightly after contrast [173]. Loss of the normal posterior pituitary bright spot is seen in all patients with diabetes insipidus [15] and infundibular thickening in over 50% [174]. Infundibular atrophy (29%) and pronounced hypothalamic mass lesion (10%) are less common.

Pituitary tuberculosis

There has been a resurgence of TB during the past three decades due to the HIV/AIDS epidemic, increased travel and migration. The annual incidence per 100,000 persons varies from four cases in the USA to over 100 cases in Asia and Africa. Approximately 10% of TB cases have CNS involvement [175], which may present as meningitis or parenchymal space-occupying lesion. Pituitary TB is extremely rare, with approximately 60 cases reported since the original 1940 description by Coleman and Meredith [176]. Females are affected more frequently than males (2:1) with a mean age at presentation of 37 years [177]. Only a third of the cases have a past or concurrent history of extracellular tubercular involvement [176]. Headache is the most common presenting symptom (91%), followed by visual disturbances (46%) and cranial nerve palsy, especially the abducens nerve (23%). Fever is common in children and rare in adults [176]. Hypopituitarism is present in 77% of the patients, without preferential involvement of any hormonal axis, and can be disproportionate to the size of the sellar lesion [178]. Hyperprolactinemia and diabetes insipidus are found in 23 and 11% of the patients, respectively [176].

The treatment of cerebral tuberculosis, like that of other forms of TB, is aimed at killing both intracellular and extracellular organisms and preventing the development of drug resistance by using several drugs in combination The first-line anti-tubercular drugs are isoniazid, pyrazinamide, ethionamide, and cycloserine which penetrate into the cerebrospinal fluid well. Rifampicin, streptomycin and ethambutol penetrate in adequate concentrations are only used when the meninges are inflamed [179]. Surgical intervention is required in cases of intracranial tuberculous empyema to reduce the mass effect, as well as when serious complications such as hydrocephalus, tuberculomas and tuberculous abscesses develop [179].

Pituitary tuberculomas are usually isointense on T1-weighted images, but can be hyperintense owing to high protein content [180]. They enhance avidly after contrast, except in areas of caseation, which appear cystic. Pituitary tuberculomas show a suprasellar extension in 74% of cases, but are limited to the sella in the remaining 26% [176,177]. The sella is enlarged and the stalk is almost always thickened owing to chronic inflammation [180]. Sometimes, the suprasellar extension can make evaluation of the
stall difficult. Other MRI findings described with pituitary TB are peripheral ring enhancement of the mass, enhancement of the adjacent dura and basal enhancing exudates owing to meningiitis [180]. Isolated stalk thickening, sellar/suprasellar calcification, apoplexy and erosion of the sellar floor have also been reported in pituitary tuberculomas [176].

The aforementioned clinical and radiological features of non-functioning pituitary masses are summarized in Table 2. Overall, it is difficult to establish before surgery a diagnosis of certainty, which can be obtained in the majority of the patients only after pathological examination of the pituitary biopsy obtained via trans-sphenoidal surgery.

**Pituitary antibodies**

The presence of immunoglobulins in the serum reacting against self-antigens is one of the cardinal features of autoimmune diseases. Autoantibodies are undoubtedly the most widely used tool to diagnose, monitor and, more recently, predict autoimmune diseases. With a few exceptions, where autoantibodies are the cause of the clinical phenotype (e.g., the acetylcholine receptor antibodies in myasthenia gravis and thyrotropin receptor antibodies in Graves disease), the role of autoantibodies in the pathogenesis of autoimmune-mediated pathology remains unknown. It has now become clear that autoantibodies are present several years before the clinical diagnosis. Pioneer studies in this regard are the ones performed by Arbuckle and colleagues in systemic lupus erythematosus [181]. The authors have taken advantage of the world’s largest serum repository, maintained by the USA Department of Defense, which has over 40 million sera collected longitudinally from military personnel. The authors have shown that lupus antibodies are present several years before the clinical diagnosis and follow a predictable course with progressive accumulation of different specificities. Independently of their role in disease initiation, there is universal agreement on the fact that autoantibodies can be used as disease markers, bystander spectators of the underlying autoimmune process.

Pituitary autoantibodies only partially fulfill this role of disease markers. The main reason for their currently low clinical utility is that the pituitary autoantigens targeted by the immune system during AH remain unknown. This lack of knowledge has hampered the development of antigen-specific antibody assays and, therefore, current approaches to detect pituitary antibodies in patient sera rely on nonantigen-specific methods, such as indirect immunofluorescence. These methods have low sensitivity and specificity, and are poorly quantitative. A discussion of pituitary antigens and antibodies have been presented in detail in previous reviews (e.g., [182–184]).

When measured by indirect immunofluorescence, pituitary autoantibodies are found in a variety of conditions, ranging in increasing frequency from normal subjects to patients with histologically proven AH (Figure 4). At present, pituitary autoantibodies remain of limited value to the clinician for differentiating pituitary masses. Nonetheless, pituitary antibodies can suggest a diagnosis of AH when histopathological examination of the pituitary is not feasible and they have been associated with impairment of pituitary secretions, such as growth hormone [185–187] and gonadotropins [188]. Further studies are needed to elucidate the role of pituitary antibodies in the differential diagnosis of pituitary masses.

**Expert commentary**

During the past 5 years, the awareness of AH has increased significantly in the medical community, mainly owing to the emergence of a new form of AH secondary to anti-CTLA-4 therapy. Advances have also been made on the clinical side with a better characterization of the various AH phenotypes and its MRI features, as well as in basic research through the generation of a mouse model of AH.

---

**Figure 4.** Prevalence of pituitary autoantibodies in healthy controls and in the following disease categories: biopsy-proven AH, clinically suspected AH, isolated deficiencies of anterior pituitary hormones, other pituitary diseases different from AH, other autoimmune diseases different from AH, and diseases of nonautoimmune pathogenesis. AH: Autoimmune hypophysitis.

Modified from [182].
Autoimmune hypophysitis: expanding the differential diagnosis to CTLA-4 blockade

Review

However, the differential diagnosis of nonfunctioning pituitary masses remains challenging and can be obtained with certainty only after an invasive surgery and pathological examination of the pituitary biopsy. It is possible that discovery of AH-associated pituitary autoantigen(s) will allow the development of immunological assays that can provide us with a further tool to use in the study of pituitary lesions.

**Five-year view**

Despite AH being first reported almost five decades ago, the pathogenesis of AH remains to be discovered or confirmed. Such a discovery will allow the development of antigen-specific antibody assays that should be useful in the differential diagnosis of nonfunctioning pituitary masses. In addition, understanding the link between CTLA-4 blockade and development of AH will promote understanding of autoimmune diseases in general.

**Financial disclosure and acknowledgments**

This work was supported by NIH grant DK080351 to Patrizio Caturegli, and by the Heidenreich-von-Siebold grant of the Georg-August-University of Göttingen, Germany to Angelika Gutenberg. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

**Key issues**

- Autoimmune hypophysitis (AH) is an increasingly recognized endocrine disease that has intriguing features, such as its temporal association with pregnancy.
- AH remains difficult to diagnose with certainty before surgery because it clinically and radiologically mimics the presentation of the other 20 or so nonfunctioning sellar masses.
- AH is the only nonfunctioning sellar mass that has an autoimmune pathogenesis. It should, therefore, be possible to distinguish AH from the other masses once the specific pituitary antigens that are targeted in AH are discovered and antibody-based assays are developed.
- In recent years, a new form of AH has emerged: the form secondary to immunological therapies that block the inhibitory molecule cytotoxic T lymphocyte antigen (CTLA)-4.
- The CTLA-4-induced form of hypophysitis is increasing the awareness of AH in the medical community, and can shed light on the mechanisms leading to AH development.

**References**

Gutenberg, Landek-Salgado, Tzou et al. 


Autoimmune hypophysitis: expanding the differential diagnosis to CTLA-4 blockade


Autoimmune hypophysitis: expanding the differential diagnosis to CTLA-4 blockade


**Websites**

201 Hypophysitis research center [http://pathology2.jhu.edu/hypophysitis](http://pathology2.jhu.edu/hypophysitis)