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REVIEWS

Opinion

The Changing Clinical Spectrum of Hypophysitis

Sabrina Chiloiro,[1] Ettore Domenico Capoluongo,[2] Tommaso Tartaglione,[3] Antonella Giampietro,[1] Antonio Bianchi,[1] Andrea Giustina,[4] Alfredo Pontecorvi,[1] and Laura De Marinis[1,*]

Hypophysitis is a rare and potentially life-threatening disease, characterized by an elevated risk of complications, such as occurrence of acute central hypoadrenalism, persistent hypopituitarism, or extension of the inflammatory process to the neighboring neurological structures. In recent years, a large number of patients have been described as being affected by hypophysitis, due to the increased administration of immuno-chemotherapies. At the present time, the heterogeneous nature of hypophysitis diagnostic criteria and of the treatment protocols makes the management of affected patients difficult. We review the current data and evidence on primary and secondary hypophysitis, in order to suggest a diagnostic and therapeutic protocol that should be focused on a multidisciplinary approach, for reaching a prompt diagnosis and an appropriate and safe treatment.

Highlights

The identification of a proper clinical context and a multidisciplinary approach are crucial for an early and univocal diagnosis of hypophysitis and for an appropriate treatment.

The natural history of hypophysitis with its acute and chronic phases guides the management, treatment, and follow-up of both primary hypophysitis (PAH) and immunotherapy-induced hypophysitis (IIH).

In the acute phase of PAH, according to the multidisciplinary evaluation of the risk/benefit ratio, the glucocorticoid immunosuppressive treatment should be suggested, for the potential recovery of pituitary function and for avoiding the development of a persistent hypopituitarism and an empty sella syndrome.

The therapeutic management of IIH has to be conducted in accordance between the oncologist and the endocrinologist, to make the optimal therapeutic choice, avoiding life-threatening conditions and improving patients' outcome.

Hypophysitis: Actual and Future Prospective

Hypophysitis is a rare inflammatory disease of the pituitary gland and represents an emerging problem, as in recent years, an increased number of affected patients has been described. However, at the moment, no consensus for early diagnosis and management has been provided. For some years, the diagnosis of hypophysitis has been conducted on the basis of the histological detection of an inflammatory infiltration in the pituitary gland. According to the histological features of the pituitary tissue, hypophysitis were classified in [1–9] as: lymphocytic, in the presence of nodular aggregations of B and T lymphocytes; granulomatous, in the presence of nodular aggregations of epithelioid histiocytes and multinucleated giant cells; xanthomatous, in the presence of lipid-rich foamy histiocytes; and necrotizing, in the presence of an immune infiltrate within a necrotic pituitary tissue.

Moreover, mixed forms were described in cases with coexistence of the typical histological features of different pathological types of hypophysitis. In recent years, IgG4-related hypophysitis was distinguished, as characterized by the presence of a mononuclear infiltration of lymphocytes and plasma cells, with >10 IgG4-positive cells per high-power field [10]. IgG4-related hypophysitis was also associated with the inflammatory involvement of many other organs, such as orbit, lymph nodes, pancreas, biliary tract, retroperitoneum, mediastinum, thyroid, genitourinary tract, salivary and lacrimal glands [11]. However, the clinical application of the histological classification is limited. In fact, at the moment, pituitary biopsy is not routinely performed and remains limited to patients with an uncertain diagnosis and in patients with an indication for neurosurgical debulking [12,13].

Hypophysitis is actually classified according to the extension of the inflammatory process and to its etiology. As shown in Figure 1, anatomical classification of hypophysitis is based on the detection of the typical radiological findings. In particular, adenohypophysitis is defined in presence of

[1]Pituitary Unit, Department of Endocrinology, Fondazione A Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Department of Molecular Medicine, Università Federico II, Naple, Italy
[3]Department of Radiology, Istituto Dermopatico dell'Immacolata, Rome and Università Cattolica del Sacro Cuore, Rome, Italy
[4]Department of Endocrinology, Università Vita Salute San Raffaele, Milan, Italy

neuroradiological signs of inflammatory involvement of the anterior pituitary gland, as the symmetrical enlargement of the adenopituitary [13]. Infundibulo-neurohypophysitis is defined in presence of neuroradiological signs of involvement of the infundibulo-neuropituitary as pituitary stalk thickening and loss of the posterior pituitary bright spot on T1-weighted images [13]. Panhypophysitis is instead defined by the presence of neuroradiological signs of involvement of the anterior, posterior pituitary lobes and infundibulum, as the symmetrical enlargement of the adenopituitary, with a homogeneous contrast enhancement, thickening of the whole pituitary stalk, and loss of the posterior pituitary bright spot on T1-weighted images [13]. According to its etiology, hypophysitis is defined as primary if the inflammation involves inherently the pituitary gland [14]. In these cases, an autoimmune etiology is assumed. Secondary hypophysitis is considered to be triggered by defined causes, as the presence of focal pituitary lesions (such as craniopharyngioma, adenoma, germinoma, and Rathke cleft cyst) [15–18] or treatment with immunomodulatory drugs [such as

*Correspondence:
Laura.DeMarinis@unicatt.it
(L. De Marinis).

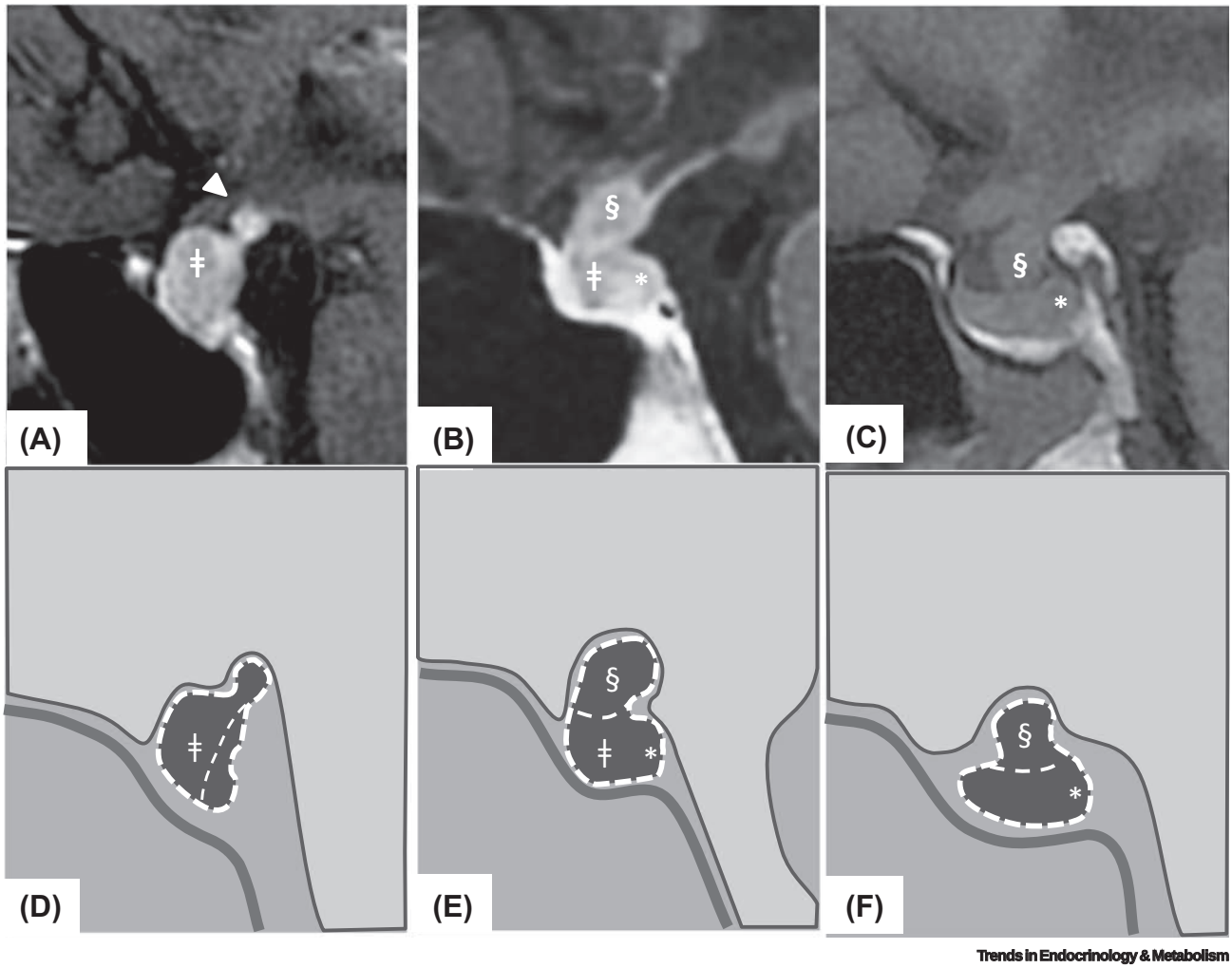

Figure 1. Neuroimaging Features of Adenohypophysitis (A, D), Panhypophysitis (B, E), and Neurohypophysitis (C, F). (A, B) Sagittal post-contrast T1-weighted magnetic resonance (MR) image. (C) Sagittal unenhanced T1-weighted MR image. (D–F) Schematic representation of three different types of hypophysitis. (A, D) Case of adenohypophysitis with (‡) enlarged adenopituitary and (arrowhead) pituitary stalk of physiological size but tending towards enlarged adenopituitary. (B, E) Case of panhypophisitis with enlargement of both neuropituitary and adenopituitary, and thickening of the whole pituitary stalk with a pseudocylindrical aspect. (C, F) Case of infundibulo-neurohypophysitis with (*) absence of physiological neuropituitary bright spot on T1-weighted images and thickening of the pituitary stalk (§) with a pseudotriangular shape.

interferon-α, ribavirin, or immune checkpoint inhibitors (ICIs)] [14,19,20]. Immunotherapy-induced hypophysitis (IIH) represents the most common form of secondary hypophysitis. Secondary hypophysitis can also occur in patients affected by systemic autoimmune diseases (e.g., sarcoidosis, granulomatosis, vasculitis, and Crohn's disease) [21–23] or infectious diseases (e.g., syphilis, tuberculosis, and fungal and viral infection in immunodepressed patients) [24,25].

In this clinical context, primary hypophysitis (PAH) represents an exclusion diagnosis [1,2]. Here, we analyze and summarize the current literature on hypophysitis, comparing primary and secondary forms, in order to formulate a potential diagnostic and treatment protocol.

Epidemiology of PAH and IIH

Epidemiological data of PAH and IIH are not conclusive. The reported annual incidence of PAH is estimated as one case per 9 million inhabitants [26]. Females are predominantly affected by adenohypophysitis, and middle-aged males and children by infundibulo-neurohypophysitis [27,28].

IIH frequency ranges from 0.7% to 15% of ICI-treated patients [29–31]. This different frequency may be influenced by different factors, such as the class of ICI, the use of ICI-associated treatments, duration of follow-up, study design, protocol for safety survey, and IIH diagnostic criteria. The prevalence of IIH is higher in patients on ICI combination treatment and in patients treated with anti-CTLA-4 antibodies, as compared to those treated with anti-PD1 antibodies [32–34]. Similarly, the time of IIH occurrence results more quickly in patients on ICI combination therapy (30 days on average) [35]. IIH occurs later in patients on treatment with anti-CTLA-4 and anti-PD-1/PD-L1 (between 2 and 5 months) [29,36,37]. However, conclusive data on the late occurrence of IIH are not available, as the follow-up in clinical trials is currently too short.

Most of the epidemiological data derive from clinical trials, in which patients with underlying autoimmune disease were usually excluded, according to the critical role of CTLA-4 in immunological homeostasis [38]. The selection of the study population represents a bias. Similarly, few reports have been published concerning patients affected by active autoimmune disease and treated with ICI [39,40]. The IIH incidence is also strongly influenced by disease diagnostic criteria [31]. The frequency of IIH is lower in cases diagnosed with new-onset hypopituitarism associated with the radiological features of hypophysitis, ranging from 1.4% to 11.8% of cases [29–31,35,41,42]. Instead, the frequency of IIH is higher in cases diagnosed only for the occurrence of new-onset hypopituitarism in the absence of radiological features, ranging from 4.2% to 13.4% of cases [29–31,35,41,42]. The interpretation of hormonal tests is influenced in these patients by several factors, such as the exogenous glucocorticoid administration, the hormonal change occurring in the chronic oncological disease, and the occurrence of other endocrine immune adverse events, such as thyroiditis. Moreover, the IIH incidence is influenced by the frequency of hormonal screening: a more frequent hormonal monitoring can improve sensitivity in IIH diagnosis.

Physiopathology of PAH and IIH

The immune checkpoint is the gate regulating the immune response that is involved in maintaining immunological homeostasis and preventing the onset of autoimmune disease [43]. Programmed death (PD)-1 is one of the representative immune checkpoint molecules. It is mainly expressed on the surface of effector T cells in tumor or peripheral tissue, B cells, antigen-presenting cells, and natural killer cells. PD-1 can selectively bind to PD-1 ligand (PD-L)1 (CD274) or PD-L2 (CD273) on the cellular surface [43], reducing the inflammatory cytokine secretion. As a consequence, the downregulation of relevant immune response causes many biological effects [43]. PD-L1 and PD-L2 are normally expressed by antigen-presenting cells and may also be present on some

tumor cells, as a mechanism to evade immune surveillance. Cytotoxic T-lymphocyte antigen (CTLA)-4 is a membrane protein receptor, expressed on the immature T cell as a homologous to CD28 and is involved in the priming phase of the cancer immunity cycle. Instead, PD-1 plays a role in an effector phase [43]. Therefore, CTLA-4 acts as a negative regulator of the anticancer immune response. The recent development of new ICIs has yielded promising results for treatment of some malignancies. ICIs promote antitumor activity. Some ICIs, such as ipilimumab, inhibit CTLA-4, acting early in the process of immune activation to increase T cell proliferation and activity. Other ICIs, like nivolumab and pembrolizumab, work as anti-PD1 drugs. Since the mechanism of inhibition can have side effects due to the involvement of these receptors in many other pathways, ICIs can also cause a wide range of immune-related adverse effects (IRAEs), such as colitis, dermatitis, hepatitis, pancreatitis, nephritis, polymyositis, uveitis, toxic epidermal necrolysis, DRESS syndrome, hemophilia A, Tolosa–Hunt syndrome, Grave's ophthalmopathy, thyroiditis, adrenalitis, and IIH. The central role of the immune cells in the develop of IIH is underlined by the lower prevalence of IIH in patients pretreated with chemotherapy [14], according to the well-known cytotoxic effect induced by systemic chemotherapy on immune cells [44]. Ipilimumab appears to be the drug that most frequently induces IRAEs. Recent evidence suggests that the occurrence of anti-CTLA-4 IIH may be not be dependent on the dose (10 vs 3 mg/kg) or number of treatment cycles [14,31,45]. It has been shown that CTLA-4 is expressed in pituitary endocrine cells and, when blocked by administration of a specific monoclonal antibody, leads to site-specific deposition of complement components, pituitary infiltration, and antibody formation, in particular anti-pituitary antibodies (APAs), that identified the most common targets in the thyrotrophic, gonadotrophic, and corticotrophic cells.

The immunological features and the detection of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and gonadotropin deficits should allow clinicians to establish a diagnosis of IIH or autoimmune hypopituitarism [43]. Similarly, among Caucasian patients diagnosed with PAH, a specific association was identified between PAH and celiac HLA haplotypes, particularly linked to DQ8. A higher frequency of APAs, anti-hypothalamus antibodies, and antinuclear antibodies (ANAs) was detected in patients who carried the CD-associated HLA haplotypes as compared to the not-carried ones [46]. Since it is well known that CTLA-4 can also play an important role in the mechanisms surrounding the immune response against gluten, it is possible to speculate that ipilimumab can trigger an inflammatory response, through hypersensitivity to gluten, leading to PAH development. This hypothesis could also be supported by the fact that PAH-affected patients carrying CD-associated HLA haplotypes showed a 3.25-fold higher risk of PAH, which reached 4.3-fold for DQ8 haplotypes. In this regard, the effect of many anti-PD1 or anti-CTLA-4 drugs could increase the reactivity of T cells when activated, induce a local inflammatory response that continues, as long as gliadin is present, and be responsible for further hypophysis damage. Further studies are necessary to confirm this type of relationship.

Diagnostic Criteria of PAH and IIH

PAH and IIH are diagnosed in most cases through clinical criteria [47], as pathological analysis of the pituitary tissue is not performed in the absence of indications for surgery. Pituitary biopsy is not routinely performed because of its invasiveness and potential risk of further deterioration of pituitary function [12,13], and remains limited to patients with an uncertain diagnosis and in cases with an indication of neurosurgical debulking, for reducing the obvious nerve compression [12,13].

PAH and IIH should be diagnosed through integration of immunological, clinical, endocrinological, and radiological features, representing an exclusion diagnosis. Hypophysitis should be suspected in patients with pituitary dysfunction or neurological/ophthalmological disorders (such as headaches and visual field defects) associated with the typical neuroradiological

features. Occurrence of new-onset headaches, hypopituitarism, and reversible radiological pituitary enlargement should suggest the diagnosis of IIH, in patients on ICI treatment, if alternative etiologies are excluded [31].

PAH is typically diagnosed during its acute phase, when the enlargement of the pituitary gland, stalk, and infundibulum, due to the inflammatory infiltrate, determines the signs and symptoms of PAH. The chronic phase of PAH is characterized by irreversible hypopituitarism, due to the development of progressive fibrosis and consequent empty sella syndrome [48]. However, onset symptoms of hypophysitis are variable and may be misunderstood for their subclinical and latent course.

IIH diagnosis is often late, as the main symptoms overlap with those of the critical illness. In PAH and IIH, the most prevalent symptoms are headaches and profound asthenia. Headaches are reported in around 68% of PAH and 61% of IIH. Asthenia is reported in around 86% of PAH and 58% of IIH [12,31,47,49–53]. Visual defects are more frequent in PAH than in IIH, since the degree of gland enlargement in IIH is typically mild and lower than in PAH [29,31,36,54–56]. The most common pituitary deficit is central hypoadrenalism in PAHs (8–86% of cases) and central hypothyroidism in IIH (86–100% of cases).

Central hypoadrenalism is reported in 50–73% of IIH and central hypothyroidism in 10–77% of PAH. Frequency of central hypogonadism ranged between 1% and 62% in PAH and from 85% to 100% in IIH. Diabetes insipidus is reported in 20–83% of PAH and is rare in IIH [12,47,49,53–55]. Growth hormone deficiency (GHD) is reported in 14–62% of PAH. GHD and central hypogonadism are diagnosed in patients affected by infundibulo-neurohypophysitis [12,13], probably due to inflammation of the stalk, which hinders the transport of hypothalamic release factors [56].

In patients with suspected hypophysitis, magnetic resonance (MR) contrast is essential to identify the typical radiological signs of disease (pituitary enlargement, pituitary stalk swelling, and absence of posterior pituitary bright spot on T1-weighted images [13]), to exclude focal lesions, evaluate the mass effect, and assess the extent of inflammation.

A symmetric pituitary enlargement is described in around 91.7% of PAH [51] and 30–100% of IIH cases [47]. Pituitary stalk thickening is reported in 33–88% of PAH [47,49,57,58] and the loss of the neuropituitary bright spot on T1-weighted images is described in 20–88% of cases [47,58]. Instead, pituitary stalk swelling and the disappearance of the neuropituitary signal are rarely reported in IIH [55], as well as compression of the optic chiasma. The typical radiological sign of IIH is mild pituitary enlargement, with a convex shape and homogeneous and hyperintense signal on T1-weighted images after gadolinium injection [29,30,35]. The radiological IIH signs can be mild and sometimes identifiable only if compared to previous MR images [30]. In IIH, pituitary enlargement resolves more rapidly than in PAH (within weeks to months) [55] and may precede the clinical diagnosis of hypopituitarism [30,55] (Figure 2). Instead, in PAH, the inflammatory process evolves slowly with progressive fibrosis and consequent empty sella [48].

Hormone Replacement Therapy in PAH and IIH

As summarized in Table 1 [59–62], hormone replacement therapy should be administered according to the hypophysitis phase. Both in the acute and chronic phases of PAH and IIH, central hypoadrenalism, diabetes insipidus, and central hypothyroidism have to be managed. As a potential life-threatening condition, central hypoadrenalism has to be promptly treated, through the oral or parental administration of hydrocortisone, according to the patient's clinical

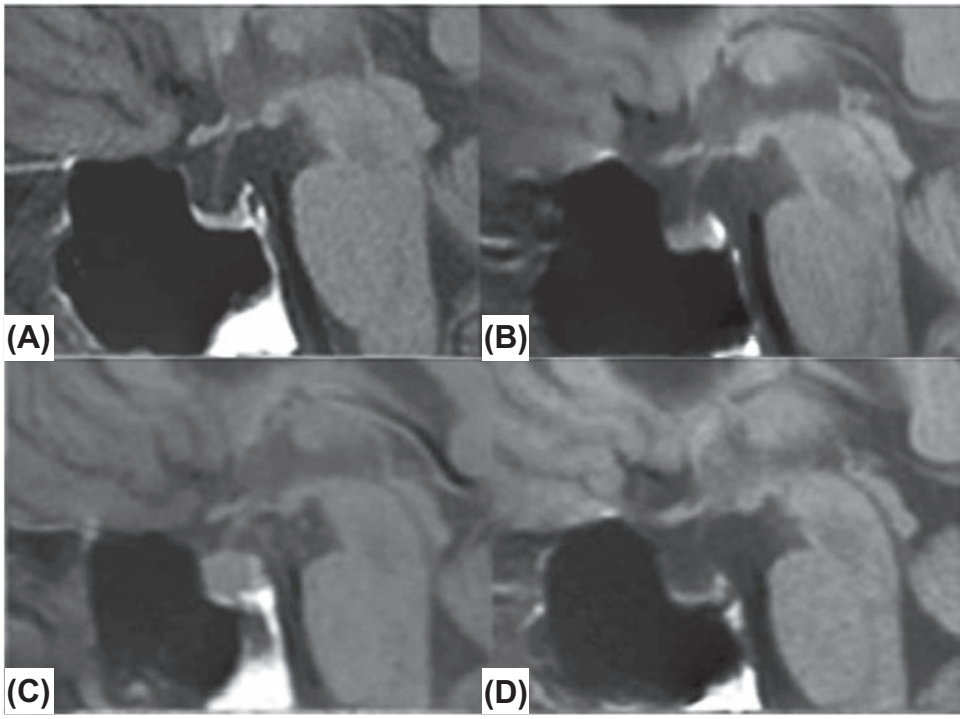

Figure 2. Sagittal T1-Weighted Magnetic Resonance (MR) Images after Medium Injection in a Case of Immunotherapy-Induced Hypophysitis. (A) MRI conducted before starting ipilimumab. (B) MRI conducted after the second cycle of ipilimumab, showing initial enlargement of the pituitary gland. (C) MRI conducted after the third cycle of ipilimumab, when the patient was diagnosed with central hypoadrenalism. (D) MRI conducted after 1 month follow-up. Abbreviations: MRI, magnetic resonance imaging.

condition [63]. Similarly, in cases of diabetes insipidus, desmopressin acetate has to be administered, to regulate serum sodium concentration, plasma and urinary osmolarity, and systemic arterial pressure [64]. In patients affected by central hypothyroidism, hormone replacement therapy should be prescribed only after the correction of hypoadrenalism: thyroid hormone replacement can worsen symptoms and facilitate adrenal crisis in the clinical setting of untreated adrenal insufficiency.

With regard to central hypogonadism and GHD, interactions between hormone replacement therapies and immune system homeostasis are not completely clarified [65,66]. A possible resolution of these pituitary deficits has been described, after PAH glucocorticoid immunosuppressive treatment [67]. Consequently, central hypogonadism and GHD should be confirmed with laboratory tests, after glucocorticoid immunosuppressive treatment and administration of these therapies may be delayed in the chronic phase of the disease. The prescription of sex hormone replacement and recombinant human (rh)GH is not indicated for the acute phase of PAH [68]. In patients with IIH, hypogonadism replacement therapy has to be prescribed with respect to the type of neoplasia. rhGH is always contraindicated.

Immunosuppressive Therapy in PAH and IIH

Immunosuppressive therapy should be considered only during the acute phase of hypophisitis in order to inhibit the inflammatory process, to reduce the compressive effects of the enlarged pituitary gland, and to avoid the development of glandular fibrosis that may cause irreversible hypopituitarism.

Table 1. Indications for Hormone Replacement Therapy, According to Hypophysitis Natural History, during the Acute or Chronic Phase of PAH and IIH [59–63]

	Phase	PAH	IIH
Central adrenal insufficiency	Acute/ chronic	Acute/chronic phase: hydrocortisone. Dose adjustment and route established according to patient's clinical conditions. Stress dose: parental injection of 50–100 mg hydrocortisone. Replacement dose: hydrocortisone from 15 to 20 mg/day in fractionated doses. Instruction for emergency corticosteroid administration and prescription of a kit for injectable high-dose corticosteroid.	
Central diabetes insipidus	Acute/ chronic	Desmopressin acetate: dosage should be adjusted according to amount of intake fluids, urinary volume, plasmatic and urinary osmolarity and sodium concentration.	
Central Hypothyroidism	Acute/ chronic	Levothyroxine (LT4) has to been administrated, after the treatment of secondary hypoadrenalism. LT4 should be prescribed at the initial dose of 0.8 μg/kg/day in young patients and in patients without history of cardiac disease. Lower initiating dose (from 12.5 to 25 μg/day) are suggested for patients older than 65 years and patients with history of cardiac disease. In many patients, full-weight-based dosing of 1.6–1.8 μg/kg/day may be needed. Dose titration should be conducted according to free T4 measurements, conducted 4 weeks after LT4 initiation. TSH monitoring is suggested as the detection of an elevated value which can suggest the improvement of central hypothyroidism or the recovery phase of the nonthyroidal illness syndrome.	
Central hypogonadism	Acute	No data supporting sex hormonal replacement therapy, after the resolution of acute phase or after the glucocorticoid immunosuppressive treatment, according to the potential recovery of gonadal function.	
	Chronic	Sex hormone replacement should be considered in men (<65 years) and premenopausal woman, if not contraindicated, as in cases of: - history of breast, prostate, endometrial cancer, or sex hormone dependent neoplasia; - diagnosis of palpable prostate nodule, prostate-specific antigen >4 ng/ml or >3 ng/ml with a risk of prostate cancer; - elevated hematocrit, history of thrombophilia, venous or arterial thromboembolism; - uncontrolled severe obstructive sleep apnea, heart failure, myocardial infarction, stroke within at least 6 months.Strict surveillance in recommended in patients with diabetes mellitus, hypertriglyceridemia, hepatic hemangioma, systemic lupus erythematosus, asthma, gallbladder disease, epilepsy, benign meningioma, porphyria cutanea tarda, intermediate or high risk of sex hormone dependent neoplasia or cardiovascular diseases.	
GHD	Acute	Not indicated	Contraindicated according to the history of active neoplastic disease.
	Chronic	rhGH is recommended, after the resolution of acute phase or after the glucocorticoid immunosuppressive treatment, if dynamic test confirm the presence of GHD.	

Glucocorticoids are considered as a first-line option for immunosuppressive treatment. Therapeutic schemes described in the literature are based on low or high doses of glucocorticoids (prednisolone 7.5–10 mg/day and 0.5–2 mg/kg/day or equivalent) [30,31,52,67,69]. The PAH and IIH outcome after glucocorticoid immunosuppressive treatment is not completely clarified [30,31]. Pituitary secretion improvement was described in 15–41% of PAH [12,13,49,52,53,67,70] and 42–64% of IIH [30,71]. Radiological improvement was seen in 36–89% of PAH [24,25,27,30,31,43,46] and 73–90% of IIH [30,71].

Among patients treated with immunosuppressive glucocorticoids, recovery of central hypogonadism, GHD, and diabetes insipidus was described in some cases of PAH [67], and of central hypothyroidism and hypogonadism in some cases of IIH [29,31]. Actual evidence of relapse of PAH is not conclusive. According to the same reports, PAH recurrence can occur in up to 38% of cases after glucocorticoid immunosuppressive therapy [49,52,67]. Moreover, some authors have suggested that even after PAH recurrence, patients treated with glucocorticoid can maintain their own pituitary function without the need of lifelong hormone replacement therapy [72].

The variable outcome between patients treated or untreated with glucocorticoid immunosuppressive therapy and relapse of pituitary inflammation may be justified by several factors, such as study design, sample size, study population selection criteria, different disease stage, treatment choice, drug dose, and definition of outcome. In PAH, some markers have been suggested as potential positive predictors of treatment outcome, such as short standing disease, presence of APAs, diagnosis of infundibulo-neurohypophysitis, and detection of diabetes insipidus and

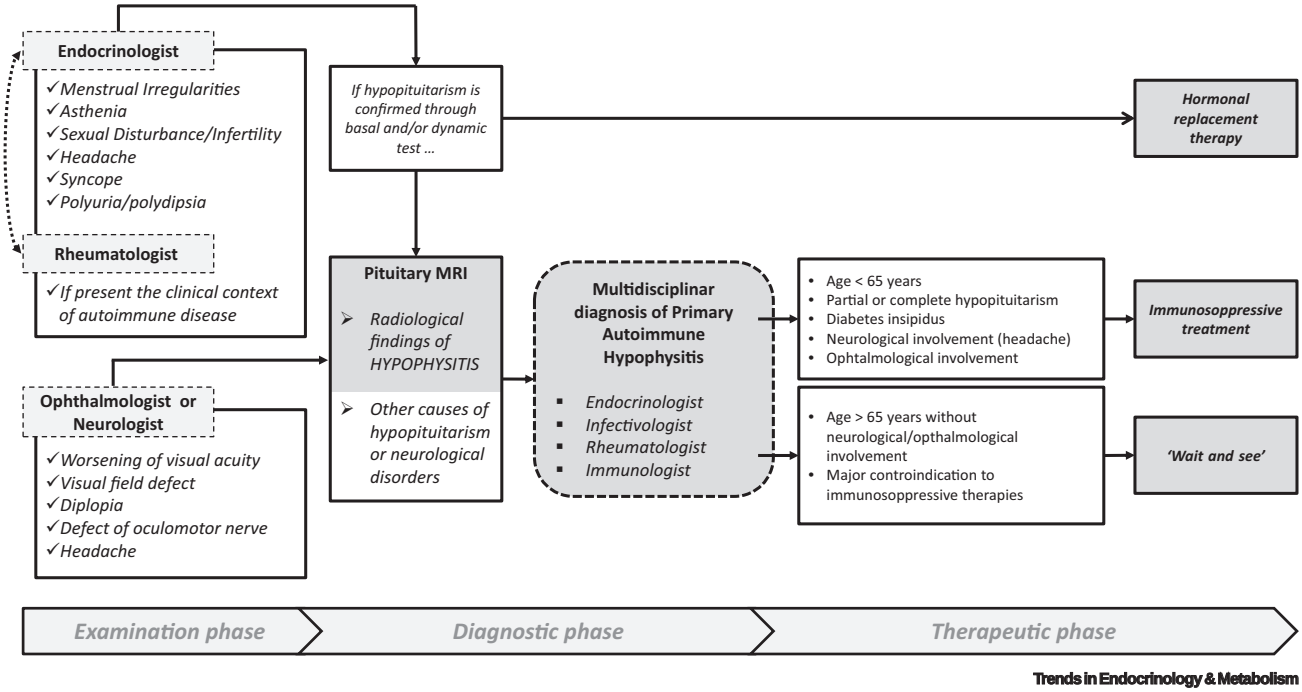

Figure 3. Flow-chart of Diagnosis and Treatment of Primary Autoimmune Hypophysitis. Abbreviation: MRI, magnetic resonance imaging.

central hypogonadism at PAH diagnosis [13,67,70]. Instead, no biomarker able to predict the benefit of glucocorticoid immunosuppressive treatment in IIH has been detected, and a history of pituitary disorders is not considered a risk factor for IIH [73]. Moreover, azathioprine, mycophenolate mofetil, methotrexate, and cyclosporine A have been successfully used in PAH resistant to corticosteroids [74]. A few cases of effective rituximab treatment of steroid-refractory PAH have been described [75]. The administration of rituximab, a monoclonal antibody that binds to CD20 of B lymphocytes, should be considered in selected cases [76], according to drug safety profile: infections were reported in around 34% of cases, persistent dysgammaglobulinemia in 25%, and B cell reconstitution in 19%. Moreover, the presence of $CD20^{+}$ lymphocytes in the pituitary inflammatory infiltrate is mandatory for treatment efficacy.

PAH and IIH Management

PAH and IIH represent a complex scenario that requires a multidisciplinary approach for diagnosis, treatment, and follow-up. As summarized in Figure 3, PAH diagnosis should be conducted according to the clinical findings, in the appropriate clinical context. Pituitary MR images play a central role in diagnosis, through the exclusion of focal pituitary lesions. Similarly, the etiological diagnosis of hypophysitis requires a multidisciplinary management. At diagnosis, infectious disease specialists and rheumatologists should exclude hypophysitis due to infective and systemic autoimmune disease, in order to orient an etiological treatment (Figure 4A). Similarly, an immunological evaluation reinforces the PAH diagnosis and its autoimmune etiology, according to the identification of APA, ANA, and extractable nuclear antibody [12]. After diagnosis of PAH, glucocorticoid immunosuppressive treatment is suggested in patients without major contraindications to those treatments, according to a multidisciplinary evaluation of the risk/benefit ratio [67] and in patients desirous of pregnancy (Figure 3). According to our personal experience [67], recovery of central hypogonadism and GHD was reached in patients treated with immunosuppressive

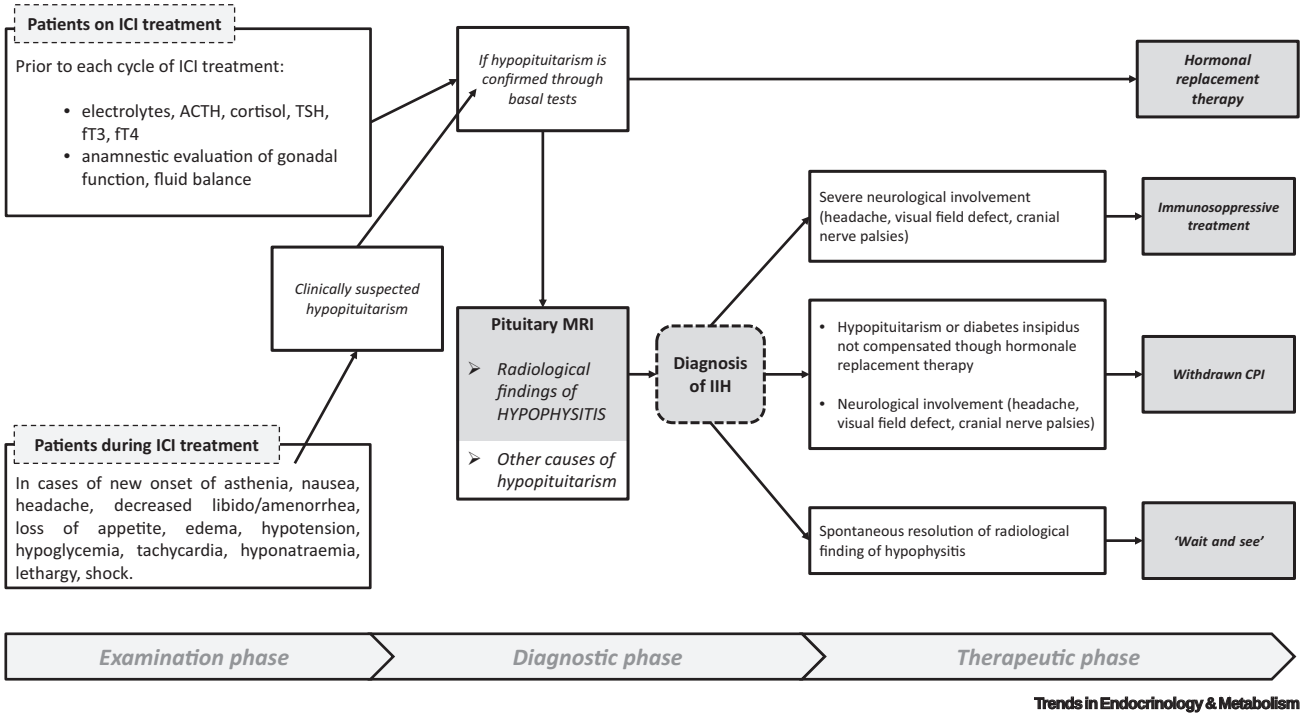

Figure 4. Flow-chart of Diagnosis and Treatment of IIH. Abbreviations: ACTH, adrenocorticotropic hormone; fT3, free tri-iodothyronine; fT4, free thyroxine; ICI, immune checkpoint inhibitor; IIH, immunotherapy-induced hypophysitis; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone

glucocorticoids. However, current guidelines or consensus on indications, duration, and dose of immunosuppressive treatment are not available. Different therapeutic schemes have been proposed, such as low or high doses of glucocorticoids (prednisolone 7.5–10 mg/day and 0.5–2 mg/kg/day or equivalent) [30,31,52,67,69]. According to our personal experience [67], 13 months' treatment with prednisone appears to be an effective and safe therapeutic option. In our clinical practice, we start glucocorticoid immunosuppressive therapy with 50 mg/day prednisone or equivalent [67]. Glucocorticoid dose is reduced by 50%, 3 months after treatment initiation, according to the improvement of clinical and radiological signs, and then dose is reduced by 50% every 2 months [67]. However, prospective trials are still required to define the optimal therapeutic choice, in terms of glucocorticoid dose and duration of treatment.

During the treatment period, endocrinologists, radiologists, and ophthalmologists have to define PAH outcome, according to clinical and morphological features. Instead, rheumatologists should manage the immunosuppressive therapy, particularly in cases unresponsive to glucocorticoids that require other classes of immunosuppressive drugs, such as azathioprine, mycophenolate mofetil, and methotrexate. Similarly in IIH, the collaboration of oncologists, endocrinologists, and radiologists is essential for reaching an early diagnosis. The clinical and laboratory evaluation of the pituitary function is recommended before each ICI cycle and in cases of a new onset of symptoms suggestive of pituitary dysfunction (Figure 4). Also in IIH, radiology plays a crucial rule in the diagnosis of hypophysitis and in exclusion of new pituitary gland or stalk metastasis.

The therapeutic management of IIH should be conducted in accordance between oncologists and endocrinologists, for making the optimal therapeutic choice. In IIH, data on the safety of glucocorticoid treatment are not conclusive. Nevertheless, a relationship between the administration

of glucocorticoids and the patients' overall survival has not been proved [30], Faje *et al.* [31] showed reduced survival rate among patients who received higher doses of glucocorticoids, suggesting a potential negative effect of this treatment on ICI efficacy. The main aim of glucocorticoid treatment in IIH is the improvement or resolution of symptoms due to the compressive effect of the enlarged pituitary gland, such as visual field defects, cranial nerve palsy, and headache [68]. Corticosteroid treatment is not systematically recommended in IIH, according to the controversial findings on the benefit and risk of this treatment, and the absence of systematic and randomized comparative studies. High-dose corticosteroids should be reserved for patients with acute IIH, with substantial mass effects, such us impingement of the optic chiasm, visual disorders, disabling headache, or cranial nerve palsy. Otherwise, patients with mild headache may be treated with low doses of corticosteroids [30,31].

In oncological clinical practice, the side effects that occur during anticancer therapies are graded through the Common Terminology Criteria for Adverse Events (CTCAE), as summarized in Table 2 [77,78]. This classification guides physicians in deciding whether to continue treatment, adjust dosage, or discontinue treatment [71,79]. CTCAE grading seems to be difficult to apply to endocrine IRAEs [73]. In most cases, the onset of new hypopituitarism or the occurrence of IIH requires the initiation of replacement treatment, that is considered a CTCAE grade 2. In these cases, according to CTCAE grading, ICI should be withdrawn [77,78]. However, according to IIH pathogenesis, drug withdrawal is not indicated in pituitary deficiency, as these endocrinopathies are usually well managed by hormone replacement therapy. Specific considerations should be made on the management of ICI treatment in IIH. ICI withdrawal should be discussed [79], taking into account the therapeutic response to ICI and IIH severity. ICIs should be interrupted during the acute phase of symptomatic IIH in patients with headache, visual field defect, cranial nerve palsy, central hypoadrenalism, central hypothyroidism, and diabetes insipidus still not compensated though hormone replacement therapy [80]. ICIs may be continued after correction of ACTH, TSH, and antidiuretic hormone deficits [29,30,36]. Continuation of ICIs is not contraindicated in the chronic phase of IIH. In the case of recurrence, switching to a different ICI is considered a treatment option [80]. A transient withdrawal of ICI is suggested until the hypopituitarism remains not compensated though an appropriate hormonal replacement therapy (Figure 4).

Table 2. Schematic Representation of the CTCAE, According to the Grade of Adverse Events and Recommendations for Management and Treatment [77,78]

CTCAE grades	Adverse event severity	Recommendations
Grade 1	**Mild**	• Close observation
Grade 2	**Moderate**	• Close observation • Withhold treatment until the resolution of symptoms and of biological disorders • Corticosteroids: prednisone at 0.5–1 mg/kg/day or equivalents, in case of symptoms persisting for >1 week
Grade 3	**Serious/ hospitalization required**	• Close observation • Withhold treatment until the resolution of symptoms and of biological disorders • Corticosteroids: prednisone at 1–2 mg/kg/day prednisone or equivalents
Grade 4	**Potentially fatal/ life-threatening**	• Close observation • Permanently discontinue treatment • Corticosteroids: prednisone at 1–2 mg/kg/day prednisone or equivalents
Grade 5	**Fatal/ Toxicity-related death**	

In both PAH and IIH, a neurosurgical debulking approach should be considered in selected cases, such as patients who are unresponsive to immunosuppressive treatment and with worsening neurological compressive symptoms, and in patients with uncertain diagnosis.

Patients' follow-up should be scheduled according to the disease phase. In the acute phase of PAH and IIH, a clinical/laboratory assessment should be conducted monthly for monitoring clinical condition, titration of hormone replacement therapy, and the occurrence of adverse events in immunosuppressive-treated cases. Pituitary MR should be scheduled 3 months after diagnosis and then every 6 months, to define the disease outcome. In cases of IIH with neurological symptoms, monthly pituitary MR is recommended. In the chronic phase of PAH and IIH, pituitary MR should be scheduled in cases of symptoms suggestive of disease recurrence.

Concluding Remarks and Future Perspectives

The heterogeneity of hypophysitis definition and the diagnostic/therapeutic protocols makes the evaluation and management of hypophysitis difficult, resulting in increased morbidity, worse outcomes, or even death. Cases of spontaneous partial and complete recovery have been documented. Univocal diagnostic criteria, treatment protocols, and outcome definitions are required for prompt diagnosis and treatment and for appropriate management of immunotherapy, avoiding life-threatening conditions and improving patients' outcome. Future researches, prospective studies, and clinical trials should address the definition of univocal diagnostic criteria for PAH and IIH, treatment indications, and therapeutic protocols (see Outstanding Questions). A multidisciplinary approach is crucial and may represent the first step for optimizing the therapeutic management of these patients. Moreover, the identification both of biomarkers able to predict treatment responsiveness and antigens of hypophysitis may be useful for developing target and personalized therapies.

Outstanding Questions

Future research should address the definition of univocal diagnostic criteria for PAH and IIH.

Prospective studies and clinical trials should be conducted for designing therapeutic protocols and defining treatment indications.

The identification of biomarkers able to predict treatment responsiveness may allow personalized treatment.

Biological and molecular studies are advocated in order to identify antigens involved in the pathogenesis of hypophysitis, for developing target therapies.

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