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Consensus

Expert opinion on pituitary complications in immunotherapy

Opinion d'expert sur les complications hypophysaires de l'immunothérapie

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Abstract

Hypophysitis is a frequent toxic endocrine side-effect of immunotherapy. Prevalence is higher with anti-CTLA-4 antibodies (4–20%) or in association with PD-1 inhibitors (8%). Diagnosis is presumptive, based on poorly specific clinical symptoms (usually, headache and asthenia) and/or hyponatremia and/or at least one pituitary deficit and/or abnormal imaging. Visual disorder or polyuropolydipsic syndrome are exceptional. In decreasing order of frequency, deficits are thyrotropic (86–100%), gonadotropic (85–100%) or corticotropic (50–73%); somatotropin deficit or abnormal prolactin level are rarer. Pituitary MRI in acute phase shows variable moderate increase in pituitary volume, ruling out differential diagnoses, especially pituitary metastasis. Treatment of corticotropin deficiency requires systematic emergency replacement therapy, with the usual modalities, while treatment of other deficits depends on clinical status and progression. Thyrotropin and gonadotropin deficits usually recover, but corticotropin deficiency persists over the long term, requiring education and specialized endocrinologic follow-up. Onset of hypophysitis does not contraindicate continuation of immunotherapy and does not usually require high dose synthetic glucocorticoids.

Recommendations

- R1: Diagnosis of hypophysis under immunotherapy is based on suggestive clinical symptoms (usually, headache or asthenia) and/or hyponatremia and/or at least one pituitary deficit and/or abnormal imaging.
- R2: Surgical biopsy for histologic confirmation of hypophysitis under immunotherapy is not indicated if there is no evidence of other pituitary pathology such as metastasis.

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- R3: In suspected hypophysitis:
  - blood ionogram should be performed;
  - hormonal work-up should include:
    - T4L (and TSH, given the risk of thyroid involvement under immunotherapy),
    - cortisolemia and ACTH (given reports of rare cases of primary adrenal insufficiency) at 8 am (except in acute cases; see R6) in the absence of glucocorticoid drug treatment, with dynamic testing according to findings,
    - LH, FSH and estradiol in non-menopausal females without oral contraception in case of menstrual disorder, or FSH in menopausal females; LH, FSH and total testosterone in males,
    - blood prolactin.

All these results are to be interpreted in the light of the context (cancer treatment, polymedication) and compared with the initial hormonal work-up (cf. R10).

- Polyuropolydipsic syndrome should systematically be screened for clinically (given reports of rare cases of diabetes insipidus).
- Screening for somatotropin deficiency is unnecessary.
- MRI should be performed, centered on the pituitary gland, with gadolinium injection, ideally in acute phase, to confirm diagnosis and rule out differential diagnoses (notably, pituitary metastasis). Normal MRI does not rule out diagnosis.

- R4: If MRI suggests hypophysitis but with no pituitary deficit, close biological monitoring of 8-am cortisolemia should be initiated, weekly for 1 month then as in usual follow-up (cf. R11). Dynamic corticotropic function test may be performed, depending on 8-am cortisolemia and clinical status.
- R5: In proven hypophysitis, high-dose glucocorticoid drugs are not systematically recommended, but may be used symptomatically for severe headache not responding to usual analgesia and/or for visual disorder.
- R6: In suspected acute corticotropin insufficiency under immunotherapy, emergency plasma cortisol assay should be performed regardless the time of day. Intravenous, intramuscular or subcutaneous 100 mg hydrocortisone hemisuccinate injection should be followed by 24 hours' continuous infusion of 100 mg hydrocortisone hemisuccinate, as in acute corticotropin insufficiency unrelated to immunotherapy, without awaiting cortisol and ACTH assay results. When clinical and biological symptoms begin to improve, oral hydrocortisone relay should be initiated at 60 mg per 24 hr divided in 3 doses, then progressively reduced to the replacement dose.
- R7: In chronic corticotropin insufficiency under immunotherapy, daily hydrocortisone dose is 15–20 mg/day in 2–3 doses per day, adapted to clinical parameters. The patient should be followed up by an endocrinologist for therapeutic education. How to adapt hydrocortisone to acute events should also be explained to the patient and the oncologist.
- R8:
  - in case of thyrotropin deficiency, levothyroxine therapy should be considered on a case-by-case basis, according to severity, clinical tolerance and/or clinical and biological progression (free T4) assessed on the evaluation at 1 month,
  - in case of gonadotropin deficiency, estroprogestative replacement in under-50 year-old females or androgen replacement in males is considered according to progression during the first 3 months' monitoring if there are no oncologic contraindications,
  - diabetes insipidus is to be treated systematically,
  - in this oncologic context, no replacement therapy for somatotropin deficiency is indicated (cf. R2).
- R9: Hypophysitis does not contraindicate continuation of immunotherapy, which may, however, be interrupted during the acute phase of symptomatic hypophysitis. Onset of hypophysitis secondary to administration of one immunotherapy molecule (anti-CTLA-4, anti-PD-1 or anti-PD-L1) does not contraindicate switching to another. History of pituitary pathology does not contraindicate immunotherapy; replacement therapy may need to be adapted.
- R10: We recommend systematic blood ionogram, and assays of 8-am cortisol (in the absence of glucocorticoid drug treatment); TSH and T4L; LH, FSH and total testosterone in males, or LH, FSH and estradiol in non-menopausal females without oral contraception in case of menstrual disorder, or FSH in menopausal females *ahead of* first immunotherapy injection. Pituitary MRI ahead of immunotherapy is not recommended.
- R11: We recommend taking an ionogram, with clinical and hormonal monitoring (8-am cortisol in the absence of glucocorticoid drug treatment, TSH, T4L, total testosterone in males and interview on menstrual disorder in non-menopausal females) at each immunotherapy course for the first 6 months. If the patient is asymptomatic and hormonal work-up is normal, monitoring should then be done every 2 months for 6 months and only in case of suggestive symptoms after 12 months. Systematic pituitary MRI during follow-up is not recommended.

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- R12: In patients developing hypophysitis, clinical and hormonal assessment (pituitary assessment to screen for new deficits and adapt treatment) should be performed at each immunotherapy course for 6 months, then in specialist consultation every 3 months for 6 months, then twice yearly. Given the possibility of hormonal functional recovery, gonadotropin and thyrotropin axis replacement therapy may, depending on clinical status, be withdrawn under specialized monitoring. Pituitary MRI should be repeated once at 3 months to rule out differential diagnosis of pituitary metastasis and assess progression of pituitary inflammation.

1. Epidemiology

Hypophysitis secondary to anticancer immunotherapy mainly affects over-60 year-old males: 77%, with 2–5–fold greater risk than in females [1,2]. Prevalence depends on the molecule used: 4–20% under ipilimumab monotherapy, vs. 0.6% under nivolumab and 0.7% under pembrolizumab [3], and about 8%, taking all grades of hypophysitis together, under associated ipilimumab/nivolumab. Ipilimumab shows dose-dependency [3], with prevalence of 17% at 10 mg/kg, 13% at 5 mg/kg and 8% at 3 mg/kg; however, no cumulative dose effect has been shown for ipilimumab [1]. When ipilimumab (3 mg/kg) is associated to vaccination (modified HLA-A*0201-restricted peptides), incidence is 9% [3]. Incidence also depends on clinical inclusion criteria in defining hypophysitis: asymptomatic forms have been reported in 45% of cases according to Scott et al. on systematic imaging monitoring [4].

Time to onset varies according to the molecule. It is very early (mean, 30 days) in combined treatments [4], around 2–3 months (range, 4 weeks to 19 months) under anti-CTLA-4 [4–8], and between 3 and 5 months under anti-PD-1/PD-L1 [3,9]. Some authors reported no onset of hypophysitis in case of associated concomitant chemotherapy or brain radiation therapy [10–12], but these findings are controversial [4].

2. Pathophysiology

Iwama et al., in a murine model of hypophysitis secondary to iterative anti-CTLA-4 injection, reported pituitary tissue infiltration by lymphocytes and circulating anti-pituitary antibodies. The same authors studied anti-pituitary antibody prevalence in a cohort of 20 patients receiving ipilimumab for melanoma or advanced prostate cancer; 7 developed hypophysitis, all showing circulating antibodies at diagnosis of hypophysitis despite negative findings prior to immunotherapy; no antibodies were found in the other 13 patients. The antibodies mainly targeted thyrotropic, FSH gonadotropic and corticotropic cells, raising the hypothesis that anti-CTLA-4 may induce pituitary toxicity if the antibody binds to a CTLA-4 molecule naturally expressed on pituitary endocrine cells [13]; the CTLA-4 antigen is indeed expressed in normal and adenomatous pituitary cells [14,15]. PDL-1 expression, analyzed in 48 pituitary adenomas, was found, with lymphocyte infiltrate, especially in functioning adenomas [15,16]; there were no data for PD-1 antigens. These cells are the site of classic complement activation with C3, C3d and C4d component deposit and an inflammatory cascade as observed in type-2 hypersensitivity. Direct ipilimumab binding to antepituitary cells may thus activate antibody-dependent cell-mediated cytotoxicity [17,18]. The involvement of complement activation may partially account for the difference in hypophysitis prevalence according to molecule: ipilimumab is an IgG1 monoclonal antibody and tremelimumab is type IgG2, both able to activate the classic complement pathway and antibody-dependent cell-mediated cytotoxicity; nivolumab and pembrolizumab, on the other hand, are IgG4 antibodies targeting PD-1, and thus cannot activate the classic complement pathway [19,20].

3. Diagnosis

Diagnosis of hypophysitis is "presumptive", as no surgery is usually performed [21,22]. It is thus based on:

- association of clinical signs, related to tumoral syndrome or hormonal deficits;
- and/or hyponatremia and proven hormonal abnormalities;
- and/or pituitary imaging abnormalities suggestive of hypophysitis [22,23].

Clinical signs are poorly specific; the most frequent are headache and profound asthenia. Visual disorder or polyuropolydipsic syndrome are exceptional [1,5,6,8,14,24]. Symptomatology is often stronger with associated anti-CTLA-4 and anti-PD-1 [4].

Hormonal deficits are often multiple at diagnosis, and associated with hyponatremia (113–134 mEq/l) in 47–50% of cases, especially in case of brain metastasis [1,4,6]. There are frequently thyrotropin (86-100%), gonadotropin (85–100%) and corticotropin deficits (50–73%). However, in case of strong clinical suspicion with normal total testosterone assay, given the usual poor nutritional status, complementary assay may be needed on bioavailable testosterone or TeBG. Thyrotropin deficit may be preceded by early progressive reduction in TSH over a period of weeks ahead of clinical and biological or radiological signs of hypophysitis [14,25]. Somatotropin deficiency or prolactin abnormality (hyperprolactinemia or prolactin collapse) are rarer [6]. Diabetes insipidus is rare: 2 cases were reported under ipilimumab (1 partial permanent and 1 resolved after immunotherapy termination) [5,26], 1 after 3 months' avelumab (anti-PDL-1), resolved 6 weeks after immunotherapy

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termination in a patient with no other pituitary deficits or signs of hypophysitis on MRI [27], and 1 under combined ipilimumab + nivolumab [28]. Deficit onset may also be progressive after diagnosis, and regular hormonal monitoring after onset of hypophysitis is recommended, notably of the corticotropic axis [1,4,6,29]. Transient ACTH-dependent hypercortisolism ahead of corticotropin deficiency was reported in 1 patient under combined ipilimumab + nivolumab therapy [30].

Gadolinium-enhanced MRI centered on the pituitary gland is the most sensitive diagnostic examination. It shows a variable (30–100%) aspect of lymphocytic hypophysitis with moderately increased pituitary volume (convex aspect), intense, sometimes heterogeneous gland enhancement on injection, and sometimes an enlarged pituitary stalk [4,6,2]. Modifications on MRI may be moderate, sometimes only identifiable by comparison with previous images [2]. MRI also rules out other pathologies in this tumoral context: metastasis, abscess, pituitary apoplexy, pituitary adenoma, infiltration-related pathology, etc. [8].

R1: Diagnosis of hypophysis under immunotherapy is based on suggestive clinical symptoms (usually, headache or asthenia) and/or hyponatremia and/or at least one pituitary deficit and/or abnormal imaging.

R2: Surgical biopsy for histologic confirmation of hypophysitis under immunotherapy is not indicated if there is no evidence of other pituitary pathology such as metastasis.

In case of MRI abnormality suggesting hypophysitis with or without associated clinical symptoms (sudden violent headache, aggravation of pre-existing headache), without pituitary deficit, close hormonal monitoring should be implemented, as onset of clinical symptoms and deficits may be secondary [1,4,14,2].

4. Treatment

High-dose oral or intravenous corticotherapy in the acute phase of hypophysitis under immunotherapy is highly controversial. Studies report no proven benefit for progression in the short term (notably, for pituitary infiltration) or in the longer term (recovery of the various pituitary axes) [8,24,2]. The treatment counters the anticancer effect of immunotherapy and may even engender side-effects requiring hospital admission: severe glucose imbalance or acute corticotropin deficiency following rapid reduction in corticotherapy dose [31]. Systematic high-dose glucocorticoid treatment in acute-phase hypophysitis following immunotherapy is therefore not recommended, but may be considered in case of severe headache, visual disorder or other autoimmune side-effects [6,31,32].

R3: In suspected hypophysitis:

- Blood ionogram should be performed.
- Hormonal work-up should include:
  - T4L (and TSH, given the risk of thyroid involvement under immunotherapy),
  - cortisolemia and ACTH (given reports of rare cases of primary adrenal insufficiency) at 8 am (except in acute cases; see R6) in the absence of glucocorticoid drug treatment, with dynamic testing according to findings,
  - LH, FSH and estradiol in non-menopausal females without oral contraception in case of menstrual disorder, or FSH in menopausal females; LH, FSH and total testosterone in males,
  - blood prolactin.

All these results are to be interpreted in the light of the context (cancer treatment, polymedication) and compared with the initial hormonal work-up (cf. R10).

- Polyuropolydipsic syndrome should systematically be screened for clinically (given reports of rare cases of diabetes insipidus).
- Screening for somatotropin deficiency is unnecessary.
- MRI should be performed, centered on the pituitary gland, with gadolinium injection, ideally in acute phase, to confirm diagnosis and rule out differential diagnoses (notably, pituitary metastasis). Normal MRI does not rule out diagnosis.

R4: If MRI suggests hypophysitis but with no pituitary deficit, close biological monitoring of 8-am cortisolemia should be initiated, weekly for 1 month then as in usual follow-up (cf. R11). Dynamic corticotropic function test may be performed, depending on 8-am cortisolemia and clinical status.

In acute corticotropin deficiency, emergency hydrocortisone treatment should be initiated, at 100 mg IV, IM or SC, then 100 mg/24 h in continuous IV perfusion, with hydration by physiologic saline in case of dehydration, hypotension and/or digestive disorder. Once clinical and hydroelectric disorders resolve, 60 mg oral hydrocortisone divided in 3 doses should be initiated and progressively reduced to 15-20 mg/day, adapted to individual clinical and biological status and needs (patient in hospital, with stress, fatigue, etc.) [33]. Corticotropic axis recovery is rare, and patient and oncologist require education

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R5: In proven hypophysitis, high-dose glucocorticoid drugs are not systematically recommended, but may be used symptomatically for severe headache not responding to usual analgesia and/or for visual disorder.

in adapting hydrocortisone dose and injecting hydrocortisone hemisuccinate in emergency or in case of intercurrent event [1,6,24,32,34,35].

R6: In suspected acute corticotropin insufficiency under immunotherapy, emergency plasma cortisol assay should be performed regardless the time of day. Intravenous, intramuscular or subcutaneous 100 mg hydrocortisone hemisuccinate injection should be followed by 24 hours' continuous infusion of 100 mg hydrocortisone hemisuccinate, as in acute corticotropin insufficiency unrelated to immunotherapy, without awaiting cortisol and ACTH assay results. When clinical and biological symptoms begin to improve, oral hydrocortisone relay should be initiated at 60 mg per 24 hr divided in 3 doses, then progressively reduced to the replacement dose.

R7: In chronic corticotropin insufficiency under immunotherapy, daily hydrocortisone dose is 15–20 mg/day in 2–3 doses per day, adapted to clinical parameters. The patient should be followed up by an endocrinologist for therapeutic education. How to adapt hydrocortisone to acute medical events should also be explained to the patient and the oncologist.

In case of thyrotropin and gonadotropin deficiency, treatment initiation is less urgent, as thyrotropin and gonadotropin axes usually recover in the months following hypophysitis under ipilimumab [1,4,6,2]. In thyrotropin deficiency, biological monitoring should be implemented, with treatment in case of aggravation or persistent deficit 1 month after diagnosis [6,2]. Levothyroxine therapy (1–1.6 μg/kg according to comorbidities) may also be considered in first line in case of severe symptomatic deficiency. In gonadotropin deficiency, estroprogestative treatment in under-50 year-old females or androgen treatment in males (if not contraindicated) should be assessed in the light of deficiency progression at 3 months. Rare cases of diabetes insipidus are to be treated systematically and immediately. For somatotropin deficiency, treatment is contraindicated by the concomitant cancerous pathology.

R8:

a. In case of thyrotropin deficiency, levothyroxine therapy should be considered on a case-by-case basis, according to severity, clinical tolerance and/or clinical and biological progression (free T4) assessed on the following cycle.

b. In case of gonadotropin deficiency, estroprogestative replacement in under-50 year-old females or androgen replacement in males is considered according to progression during the first 3 months' monitoring if there are no oncologic contraindications.

c. Diabetes insipidus is to be treated systematically.

d. In this oncologic context, no replacement therapy for somatotropin deficiency is indicated (cf. R2).

In case of hypophysitis, immunotherapy can be continued after adapted treatment of hormonal deficits [6,8,14,2,32]. Interrupting immunotherapy has no impact on the natural history of hypophysitis [2]. Data are lacking on any extra risk of hypophysitis associated with pituitary pathology prior to initiation of immunotherapy: in such cases, close monitoring of the previously achieved hormonal balance is necessary, and may lead to adjustment of replacement therapy doses.

R9: Hypophysitis does not contraindicate continuation of immunotherapy, which may, however, be interrupted during the acute phase of symptomatic hypophysitis. Onset of hypophysitis secondary to administration of one immunotherapy molecule (anti-CTLA-4, anti-PD-1 or anti-PD-L1) does not contraindicate switching to another. History of pituitary pathology does not contraindicate immunotherapy. Replacement therapy may need to be adapted.

5. Monitoring

5.1. *Before initiating immunotherapy*

5.2. *During immunotherapy*

Given the frequency of hypophysitis under immunotherapy, systematic screening for corticotropin, thyrotropin and gonadotropin insufficiency is recommended. Clinical signs of hypophysitis are non-specific and may be related to the cancer; systematic biological exploration is therefore needed. Interviewing on polyuropolydipsic syndrome is enough to screen for diabetes insipidus, posterior pituitary involvement being rare in immunotherapy-induced hypophysitis [36]. The literature

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R10: We recommend systematic blood ionogram, and assays of 8-am cortisol (in the absence of glucocorticoid drug treatment); TSH and T4L; LH, FSH and total testosterone in males, or LH, FSH and estradiol in non-menopausal females without oral contraception in case of menstrual disorder, or FSH in menopausal females *ahead of* first immunotherapy injection. Pituitary MRI ahead of immunotherapy is not recommended.

review discussed in the "Diagnosis" section (above) showed that most cases of hypophysitis have onset within 6 months [7,27–29]. Pituitary MRI is performed only in case of pituitary deficiency. Impaired visual field and acuity are exceptional [14], and visual assessment is not recommended in the absence of any visual signs or optic chiasm compression on MRI.

R11: We recommend taking an ionogram, with clinical and hormonal monitoring (8-am cortisol in the absence of glucocorticoid drug treatment, TSH, T4L, total testosterone in males and interview on menstrual disorder in non-menopausal females) at each immunotherapy course for the first 6 months. If the patient is asymptomatic and hormonal work-up is normal, monitoring should then be every 2 months for 6 months, and in case of suggestive symptoms after 12 months. Systematic pituitary MRI during follow-up is not recommended.

5.3. After onset of hypophysitis

Pituitary deficit recovery is variable and, conversely, new deficiencies may occur secondarily. Min et al., in a cohort study with mean 33 months' follow-up, reported normalization of natremia in 92% of cases [2]; corticotropin deficit persisted in 86–100% of cases, compared to 13–36% for thyrotropin and 13–53% for gonadotropin [6,2]; corticotropin and gonadotropin levels recovered in 10–15 weeks [2]. Pituitary hypertrophy resolves in 73% of cases [2]. As the main differential diagnosis is pituitary metastasis, MRI should be repeated 3 months after diagnosis: if pituitary lesion size has not increased, metastasis can be ruled out.

Disclosure of interest

The authors declare that they have no competing interest.

R12: In patients developing hypophysitis, clinical and hormonal assessment (antepituitary assessment to screen for new deficits and adapt treatment) should be performed at each immunotherapy course for 6 months, then in specialist consultation every 3 months for 6 months, then twice yearly. Given the possibility of hormonal functional recovery, gonadotropin and thyrotropin axis replacement therapy may, depending on clinical status, be withdrawn under specialized monitoring. Pituitary MRI should be repeated once at 3 months to rule out differential diagnosis of pituitary metastasis and assess progression of pituitary inflammation.

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