HYPOPHYSITIS: DIAGNOSIS AND TREATMENT

Dr. Natthapon Kaewprasert

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Review | M N Joshi and others | Hypophysitis | 179:3 | R151–R163

MECHANISMS IN ENDOCRINOLOGY

Hypophysitis: diagnosis and treatment

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Abstract

Hypophysitis is a rare condition characterised by inflammation of the pituitary gland, usually resulting in hypopituitarism and pituitary enlargement. Pituitary inflammation can occur as a primary hypophysitis (most commonly lymphocytic, granulomatous or xanthomatous disease) or as secondary hypophysitis (as a result of systemic diseases, immunotherapy or alternative sella-based pathologies). Hypophysitis can be classified using anatomical, histopathological and aetiological criteria. Non-invasive diagnosis of hypophysitis remains elusive, and the use of currently available serum anti-pituitary antibodies are limited by low sensitivity and specificity. Newer serum markers such as anti-rabphilin 3A are yet to show consistent diagnostic value and are not yet commercially available. Traditionally considered a very rare condition, the recent recognition of IgG4-related disease and hypophysitis as a consequence of use of immune modulatory therapy has resulted in increased understanding of the pathophysiology of [illegible]

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INTRODUCTION

- Hypophysitis is a rare condition, an incidence of hypophysitis (all type combined) to be about 1 in 9 million.
  - But underestimate, particularly IgG4-related disease.
- The first case of autoimmune-mediated hypophysitis was descripted by Goudie and Pinkerton in 1962. Thus, the pituitary gland became the fourth endocrine gland to have demonstrated susceptibility to autoimmune mediated damage.

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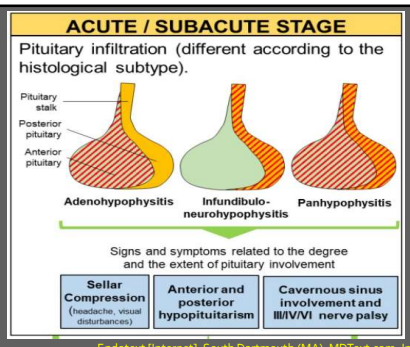

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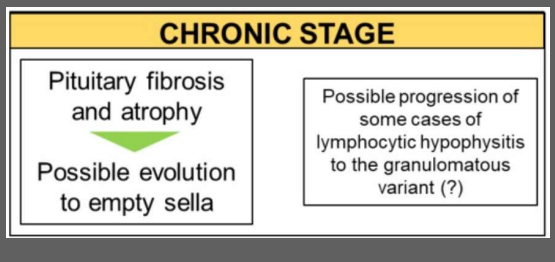

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RULE OUT SECONDARY HYPOPHYSITIS

Table 2 Conditions predisposing to the development of hypophysitis.

Autoimmune conditions
- Systemic lupus erythematosus (SLE)
- Autoimmune polyglandular syndrome (APS)

Systemic inflammatory disorders
- Sarcoidosis
- Granulomatosis with polyangitis
- IgG4-disease
- Other granulomatous (Crohn's, Takayasu's, Castlemans' disease)

Drug induced
- Immune checkpoint therapy (CTLA4 Ab, PD-1 Ab)
- Interferon α

Infiltrative lesions
- Langerhans cell histiocytosis
- Erdheim–Chester disease

Local tumour effect (Sellar diseases)
- Rupture of Rathke's cleft cyst
- Germinoma

Infection
- Tuberculosis
- Syphilis
- Fungal infections

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PRIMARY HYPOPHYSITIS

Table 1 Classification of primary hypophysitis (adapted and modified from(91)).

(a) Based on anatomy
- Lymphocytic adenohypophysitis
- Lymphocytic infundibuloneurohypophysitis
- Lymphocytic pan-hypophysitis

(b) Based on histology
- Lymphocytic hypophysitis
- Granulomatous hypophysitis
- Xanthomatous hypophysitis
- Plasmacytic/IgG4-related hypophysitis
- Necrotising hypophysitis
- Mixed forms (lymphogranulomatous, xanthogranulomatous)

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Classification of hypophysitis

Primary	Secondary
• Lymphocytic hypophysitis • Granulomatous hypophysitis • Xanthomatous hypophysitis • IgG-4 mediated (plasmacytic) hypophysitis (isolated or systemic) • Necrotizing hypophysitis • Mixed forms (lymphogranulomatous;xanthogranulomatous)	**AIH associated with other endocrinopathies**: - Autoimmune Polyglandular Syndrome – I, II, III, IV - Autoimmune thyroid disease (Hashimoto and Graves' disease) - Autoimmune adrenalitis - Type 1 diabetes mellitus **AIH associated with systemic diseases**: - Erdheim-Chester disease - Rheumatologic conditions (e.g.: sarcoidosis, Sjogren's syndrome, SLE etc.) - Vasculitides (e.g.: temporal arteritis) - Primary biliary cirrhosis - Atrophic gastritis - Optic neuritis - Myocarditis - IgG4-related disease - **Langerhans cell histiocytosis** - Rosai-Dorfman disease - Tolosa-Hunt syndrome - Cogan's syndrome - Thymoma (anti-Pit-1 antibody syndrome) **AIH secondary to Drugs** - **Immune checkpoint inhibitors: CTLA4 Ab, PD-1 Ab** - Interferon-α - Ribavirin - Ustekinumab **AIH secondary to infections** - Tuberculosis - Syphilis - Viruses - Parasites - Abscesses
AIH secondary to sellar and/or suprasellar lesions - **Germinoma** - Rathke's cleft cyst - Craniopharyngioma - Pituitary adenoma - Pituitary apoplexy - Pituitary hyperplasia - Primary pituitary lymphoma - Gliomas - Meningiomas - Pituicytomas - Chordomas - Teratomas - Dermoids - Epidermoids	

Ipilimumab
Nivolumab
Pembrolizumab

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CLINICAL PRESENTATION

SIGNS AND SYMPTOMS AT DIAGNOSIS

Adenohypophysitis (~65% of cases)	Infundibulo-neurohypophysitis (~10% of cases)	Panhypophysitis (~25% of cases)	All forms *
Headache: 53% Visual disturbances: 43% Adrenal insufficiency: 42% Hyperprolactinemia: 23% Hypothyroidism: 18% Hypogonadism: 12% Lactation failure: 11% Polydipsia/polyuria: 1%	Polydipsia/polyuria: 98% Headache: 13% Adrenal insufficiency: 8% Hyperprolactinemia: 5% Hypogonadism: 3% Visual disturbances: 3% Hypothyroidism: 0% Lactation failure: 0%	Polydipsia/polyuria: 83% Headache: 41% Adrenal insufficiency: 19% Visual disturbances: 18% Hypothyroidism: 17% Hyperprolactinemia: 17% Hypogonadism: 14% Lactation failure: 5%	Headache: 47% Adrenal insufficiency: 35% Polydipsia/polyuria: 35% Visual disturbances: 31% Hypothyroidism: 16% Hypogonadism: 20% Hyperprolactinemia: 20% Lactation failure: 8%

. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519842/

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PITUITARY HORMONE ABNORMALITIES AT DIAGNOSIS

Adenohypophysitis (~65% of cases)	Infundibulo-neurohypophysitis (~10% of cases)	Panhypophysitis (~25% of cases)	All forms
ACTH deficiency: 56% TSH deficiency: 44% FSH/LH deficiency: 42% GH decreased: 26% Hyperprolactinemia: 25% Hyperprolactinemia: 23% *** ADH deficiency: 0%	ADH deficiency: 98% FSH/LH deficiency: 8% ** Hyperprolactinemia: 5% *** Hyperprolactinemia: 0% ACTH deficiency: 0% TSH deficiency: 0% GH decreased: 0% **	ADH deficiency: 95% GH decreased: 51% FSH/LH deficiency: 47% ACTH deficiency: 46% Hyperprolactinemia: 40% *** TSH deficiency: 39% Hyperprolactinemia: 16%	ACTH deficiency: 60% FSH/LH deficiency: 55% TSH deficiency: 52% ADH deficiency: 39% GH decreased: 38% Hyperprolactinemia: 37% Hyperprolactinemia: 26%

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.
* Other possible symptoms at diagnosis include weight gain (18%) and temperature dysregulation (rare) (23,24).
** Some case series have reported a high prevalence of GH and FSH/L deficiency in patients with infundibulo-neurohypophysitis (25).
*** Hyperprolactinemia may be related to stalk compression (disconnection hyperprolactinemia) or to the immune-mediated destruction of prolactin-secreting cells.

. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519842/

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PREVALENCE

HISTOPATHOLOGY FORMS OF PRIMARY HYPOPHYSITIS
Lymphocytic hypophysitis (68%)
Granulomatous hypophysitis (20%)
Xanthomatous hypophysitis (3%)
IgG4-related (plasmacytic) hypophysitis (4%) *
Necrotizing hypophysitis (<1%)
Mixed forms (lymphogranulomatous; xanthogranulomatous).

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INVESTIGATION

- Biochemistry
  - Full early morning pituitary hormone
    - Prolactin
    - GH, IGF-1
    - Cortisol, ACTH
    - FSH, LH, Estradiol (pre-menopause), Testosterone
    - Thyroxine, TSH,
    - Plasma/urine osmolarity, Electrolyte

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INVESTIGATION

- Immunology
  - Identify Pituitary Ab can be implicated in the causation of hypophysitis
    - Serum anti-pituitary antibodies have a low sensitivity and specificity.
    - These tests are not currently part of routine practice.
  - Other disease specific antibodies (such as ANA, ds-DNA, ANCA) may be useful in the assessment of secondary hypophysitis
  - Autoimmune thyroid disease (the commonest co-associated) present in only 8% of patients with autoimmune hypophysitis

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Table 3 Investigations for suspected hypophysitis (excluding histology).

Suspected conditions	Investigations
Lymphocytic hypophysitis	Thyroid antibodies (TPO) Anti-nuclear antibody Anti-Ro, anti-La, anti-SSa, anti-Ds-DNA (if concomitant autoimmune features present) Pituitary antibody
Granulomatous lesions	Chest X-ray, interferon gamma assay if history of travel and tuberculosis suspected Serum ACE levels if sarcoidosis suspected ANCA antibodies CSF analysis for glucose, protein, oligoclonal bands, ACE CT and scintigraphy
IgG4-related disease	Immunoglobulin levels, particularly IgG4 FDG PET for disease activity
Langerhan cell histiocytosis (LCH)/Erdheim–Chester disease (EDH)	Skeletal survey, whole body bone scan FDG PET for disease activity
Germinoma (if considered as differential to hypophysitis)	Serum and CSF AFP (alpha-fetoprotein) and HCG (human chorionic gonadotropin)
Other infiltrative/infectious aetiologies	LDH (lactic acid dehydrogenase), urine analysis Imaging CSF analysis (cytology, oligoclonal bands)

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INVESTIGATION

- Histology
  - Obtaining tissue sample might also not be practical for other reasons, including spontaneous resolution or regression, response to initial medical management such as steroid therapy or difficulty in obtaining patients.
  - IHC: CD45 (leukocyte common antigen), CD3 (T-cells), CD20 (B-cells), CD68 (macrophages), and CD138 (plasma cell)

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INVESTIGATION

- Radiology
  - MRI with GAD (Investigation of choice)
    - Intense and homogenous enhancing gland with no obvious stalk deviation
    - Absence of posterior bright spot, particularly, in patients presenting with DI
    - Symetrical suprasellar extension and enhancement of the adjacent dura referred as 'dural tail'
    - Less common, presence of an empty sella.

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MRI	Primary hypophysitis	Pituitary adenoma
Pre-gadolinium	ACUTE / SUB-ACUTE PHASE: Homogeneous pituitary enlargement with symmetrical suprasella expansion; Suprasella extension with compression and displacement of chiasm; Stalk thickened but not deviated; * Loss of bright spot of the neurohypophysis in case of involvement of the posterior pituitary. ** CHRONIC PHASE: Pituitary atrophy; Empty sella.	Microadenoma (<1cm): unilateral, asymmetric endosella mass; Macroadenoma (>1cm): inhomogeneously expanding pituitary mass with asymmetrical suprasella expansion; Compression and displacement of chiasm (macroadenoma); Contralateral deviation of the stalk; The bright spot of the neurohypophysis can be usually seen. **
Post-gadolinium	Intense and homogeneous enhancement of the pituitary mass. Cystic areas have been described, especially in the xanthomatous variant; Dural tail sign can be present (thickening of the enhanced dura that resembles a tail extending from a mass). ***	Slight, delayed and inhomogeneous enhancement. Cystic and necrotic areas are frequently observed in macroadenomas; Dural tail usually absent. ***

. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519842/

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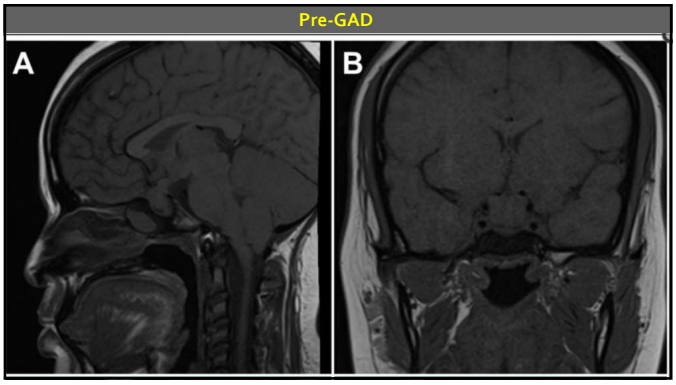

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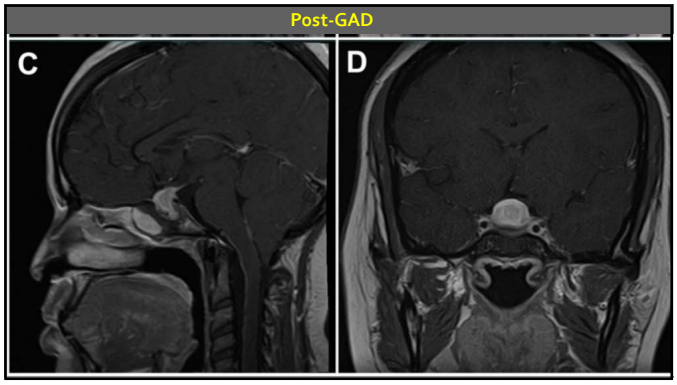

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APPROACH HYPOPHYSITIS

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CLINICAL SUSPICIOUS

- Headache and visual disturbance
- Symptoms of hypopituitarism (Especially DI)
- Known case IgG4 related disease
- Previous hypophysitis
- On immunotherapy
- MRI with characteristic feature if hypophysitis

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WORK UP

- History and examination (for rule out secondary cause)
- MRI with GAD
- Pituitary hormone
- Electrolyte BUN Cr and serum osmolarity
- CXR, Bone survey
- B-HCG, AFP
- ANA, ANCA, ALP, LDH, ESR, CRP, Anti-TPO, Pituitary Ab
- Consider biopsy

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DIAGNOSIS AND TREATMENT

- Hypophysitis confirmed vs suspected hypophysitis (full pituitary team discussion)
  - Treatment DI and hypopituitarism
  - Consider withdrawal of agents (drug induced hypophysitis)
  - Consider treatment to reduce mass effect
    - Surgery (histology)
    - Steroid
    - Medication: Azathioprine, MTX, MMF, Rituximab
    - Radiotherapy

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TREATMENT

- No strong evidence base for management recommendations
- Acute phase of hypophysitis: may require primary treatment
- Chronic or burn out phase of hypophysitis: only treatment of hypopituitarism
- The main objectives of treatment
  - Manage of pituitary hormone deficiencies
  - Reduce the inflammatory pituitary enlargement with associated mass-related consequences

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TREATMENT

- 1. Surgery
- 2. Anti-inflammatory medical therapy
- 3. Conservative management
- 4. Radiotherapy

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TREATMENT

- 1. Surgery
  - Provides a histological diagnosis to guide future management and excludes the diagnosis of tumor
  - In a large German cohort, surgery for hypophysitis
    - Significant resolution of symptoms such as headaches and visual disturbances.
    - Rate of recurrence if the lesion (11-25%)
    - Post operative follow up showed the development of pituitary insufficiencies after gross total resection compared to biopsy or partial resection.

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TREATMENT

- 2. Anti-inflammatory medical therapy
  - Glucocorticoid therapy forms the cornerstone of medical management.
  - Initial good response to steroid therapy but the overall recurrence rate has been reported to be high. (up to 38%)
  - Long term steroid leads to increasing adverse effects and limits the use of this strategy.
  - Alternative immunosuppressive agents: Azathioprine, Rituximab (monoclonal antibody)

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TREATMENT

- 3. Dopamine agonist
  - Hyperprolactinemia affects a minority of cases in the acute phase of the pituitary inflammation
  - Some authors have reported the possibility of prolactin modulating autoimmunity and the use of dopamine agonists
  - Benefit effect of long-term dopamine agonist treatment is till uncertain.
  - Provide symptomatic relief (from galactorrhea and/or hypogonadism)

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FOLLOW UP

- Early assessment of treatment response with Pituitary MRI and pituitary hormone
- Consider escalating of immunosuppressive or radiotherapy if clinical and radiological are stable

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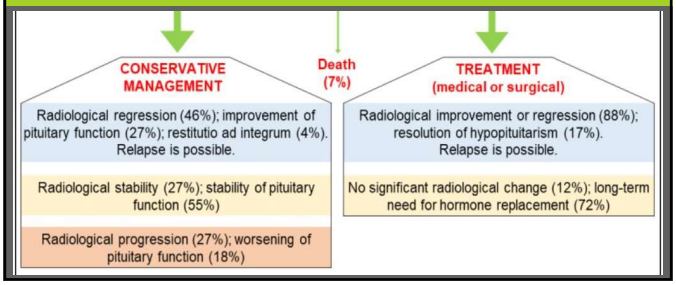
PROGNOSIS OF DISEASE



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SPECIFIC CONDITIONS

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	Lymphocytic	Granulomatous	Xanthomatous	IgG4-related	Necrotizing
Prevalence	The most common subtype (68%).	The second most common subtype (20%).	Very rare (3%).	Very rare (4%). Higher prevalence in Japan and Korea.	Extremely rare (<1%).
Gender predominance	Female, ~3:1	Female, ~3:1	Female, ~3:1	Male, ~2:1	Male, ~3:1
Association with pregnancy	Yes. ~70% of patients present during pregnancy or postpartum.	No	No	No	No
Mean age at presentation	4th decade (females). 5th decade (males)	5th decade	4th decade	7th decade	Four cases reported (aged 12, 20, 33 and 39)
Histopathology	Diffuse lymphocyte infiltration (primarily T cells) of the pituitary gland. Lymphoid follicles can be observed and occasional plasma cells,	Large numbers of multinucleated giant cells and histiocytes with granuloma formation.	Foamy histiocytes (lipid-rich macrophages) without the presence of granulomas. Plasma cells and small round mature lymphocytes are also observed.	Extensive gland infiltration by plasma cells with a high degree of IgG4 positivity. Storiform fibrosis is observed *. Pituitary	Diffuse non-hemorrhagic necrosis with surrounding lymphocytes, plasma cells and eosinophils.

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1. LYMPHOCYTIC HYPOPHYSITIS (LH)

- Most common (68%)
- It shows a striking temporal association with pregnancy, with ~70% of cases in women presenting during pregnancy or postpartum.
- Histology: Infiltration of pituitary gland with lymphocyte and plasma cells

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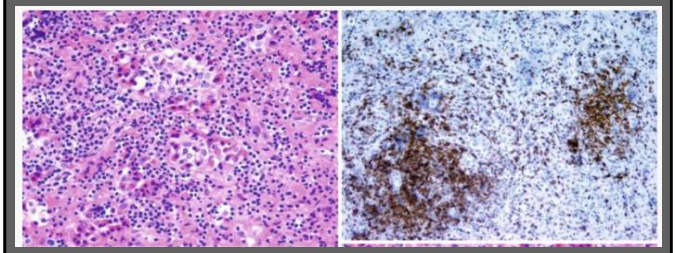

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1. LYMPHOCYTIC HYPOPHYSITIS (LH)

- Presentation: Asymptomatic, hypopituitarism, cranial nerve palsies due to mass effect or more serious complications like adrenal crisis.
- Most common hormone deficiency is of ACTH
  - ACTH -> TSH/Gn -> GH
- Diagnosis of exclusion after other forms of primary pituitary failure and secondary hypophysitis are excluded

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1. LYMPHOCYTIC HYPOPHYSITIS (LH)

- Treatment
  - Hormonal supplement
  - Conservative treatment: no mass effect
  - Medications
    - Steroid during acute phase (good response)
    - IVMP or high dose oral steroid
  - Surgery is indicated for non responders, mass effect, headache, visual failure, or when a tissue diagnosis is considered important
  - Radiotherapy: useful when there is relapse of disease

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2. GRANULOMATOUS HYPOPHYSITIS

- The Second commonest type (20%)
- Primary (idiopathic), secondary to systemic pathology such as sarcoidosis, tuberculosis or granulomatosis with polyangitis (Wegener's)
- Histology: presence of multinucleated giant cells, histiocytes, lymphocytic infiltration (granulomatous change from lymphocytic inflammatory processes.

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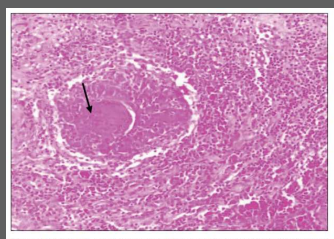

Figure 2: H and E, ×10 showing an effacement of alveolar architecture of pituitary gland by well-defined epitheloid granulomas (center) composed of multinucleate giant cells (arrow) and lymphocytes. Inflammatory infiltrate comprising predominately lymphocytes and histiocytes and occasional eosinophils is noted surrounding the granulomas and pituicytes

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2. GRANULOMATOUS HYPOPHYSITIS

- Clinical presentation: more severe with higher incidence of visual symptoms compared to LH
  - Fever, nausea, vomiting
  - In the review of 31 patients (Gonadotropin deficiency was present in 100%)
- Radiologic: not help differentiated between types
- Glucocorticoid: less effective compared with LH
- Surgical resection lead to better symptom resolution

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3. XANTHOMATOUS HYPOPHYSITIS

- The rarest of the histological types (only 18 case have been reported)
- A possible extension of the autoimmune or lymphocytic spectrum
- Clinical : milder and visual compromise is rare
- Histology: Macrophage infiltration (lipid laden macrophages) CD68+
- Radiologic: Cystic sellar masses on MRI and enhance on the post-gadolinium contrast images.
- Glucocorticoid: less effective compared with LH
- Most lesions are treated with surgery

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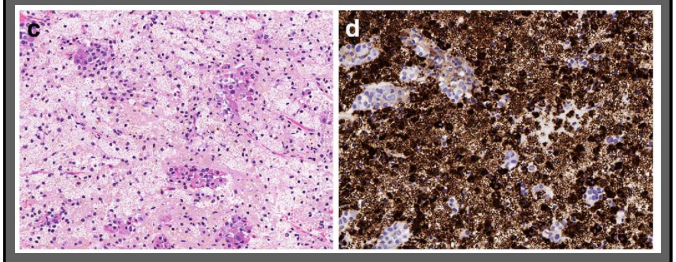

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4. IgG4-RELATED HYPOPHYSITIS

- The first case was reported in 2004.
- Recent retrospective histological review of cases.
  - LH reclassified as IgG4 hypophysitis
- The condition commonly presents as pseudo-tumor lesion with IgG4-dominant plasmacytic infiltration of multiple organ
- Present in elderly populations with male predominance
- IgG4 related hypophysitis co-existing with retroperitoneal fibrosis

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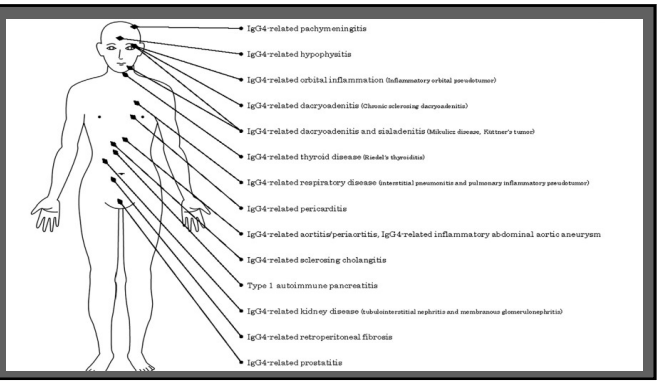

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4. IgG4-RELATED HYPOPHYSITIS

- Histologic
  - Dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis.
  - Ten IgG4-positive cells per high power field and a ratio of IgG4/IgG-positive cells of more than 40%
- Serum levels of IgG4 are not sensitive or specific for IgG4-RD and elevated levels tend to normoalise with steroid therapy
- Radiologic: no distinct features form other types

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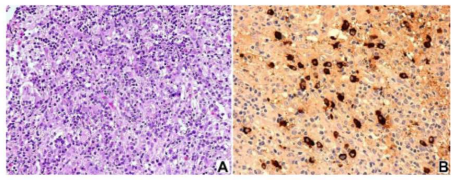

Figure 4 (A) Specimen mainly consisting of neurohypophysial tissue by lymphocytes, plasma cells, and eosinophils with stromal edema and mild fibrosis (100×); (B) a fair number of IgG4 immunoreactive plasma cells according to immunohistochemical study (400×). Ig = immunoglobulin.

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4. IgG4-RELATED HYPOPHYSITIS

- FDG PET in IgG4-RD to characterise systemic involvement of tissues
- Hormone deficit
  - Isolated diabetes insipidus was diagnosed in 12 (15.8%) cases.
  - Anterior pituitary hormone deficiency
    - Gonadotropin was the most commonly deficient hormone 68.4%, followed by ACTH (63.2%), TSH (59.2%), GH (48.7%), and prolactin (42.1%).
  - Panhypopituitarism (59.7%)

Clinical Characteristics of 76 Patients with IgG4-Related Hypophysitis: A Systematic Literature Review, International Journal of Endocrinology Volume 2019

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4. IgG4-RELATED HYPOPHYSITIS

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  - Panhypopituitarism (59.7%)

Clinical Characteristics of 76 Patients with IgG4-Related Hypophysitis: A Systematic Literature Review, International Journal of Endocrinology Volume 2019

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Other IgG4-related diseases	Number of cases	Frequency (%)
Retroperitoneal fibrosis	22	26.2
Mikulicz's disease, Küttner's tumor	21	25.0
Lymph node swelling	20	23.8
Lung inflammatory pseudotumor interstitial pneumonia	17	20.2
Autoimmune pancreatitis	12	14.3
Tubulointerstitial nephritis, kidney inflammatory pseudotumor	10	11.9
Hypertrophic pachymeningitis	7	8.3
Orbital pseudotumor iridocyclitis	7	8.3
Liver inflammatory pseudotumor	3	3.6
Nasal sinus inflammatory pseudotumor	2	2.4
Sclerosing cholangitis	2	2.4
Riedel's thyroiditis	1	1.2
Inflammatory aneurism	1	1.2
Gastric wall thickness	1	1.2
Iliopsoas muscle	1	1.2
Prostatitis	1	1.2

Pituitary (2017) 20:282–291

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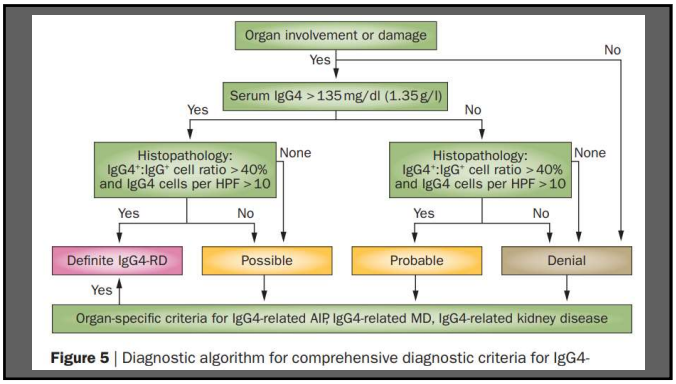

Figure 5 | Diagnostic algorithm for comprehensive diagnostic criteria for IgG4-

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TABLE 1: Diagnostic criteria for IgG4-related hypophysitis.

1. Histopathology mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells per high-power field
2. Sellar mass and/or thickened pituitary stalk on pituitary MRI
3. Biopsy-proven involvement in other organs (association with IgG4-positive lesions in other organs)
4. Elevated serum IgG4 levels (>140 mg/dl)
5. Rapidly reduction of the pituitary mass and symptom improvement with steroids

When any of the following is fulfilled, criterion 1 only, criteria 2 + 3, or criteria 2 + 4 + 5.

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4. IgG4-RELATED HYPOPHYSITIS

- Treatment
  - Currently, there was no clear standard for the treatment of IgG4-RH. Steroid therapy was the first-line treatment.
  - initial dose usually 0.6 mg/kg/day, It continued for 1-2 months.
  - Dose was tapered to a maintenance dose (2.5–5 mg/day). over a period of 2-3 months, with a taper of 5 mg every 1-2 weeks.
  - If relapse disease, the treatment can combine with immunosuppressive (rituximab, azathioprine, methotaxate and cyclosporin
  - Surgery is indicated for non responders, mass effect, headache, visual failure or need tissue diagnosis

Clinical Characteristics of 76 Patients with IgG4-Related Hypophysitis: A Systematic Literature Review, International Journal of Endocrinology Volume 2019

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5. LANGERHANS CELL HISTIOCYTOSIS

- Incidence of 1-2 cases per million in adults, it is more commonly reported in the pediatric population.
- Clinical: ranging from a self-limiting course to a rapidly progressive form.
  - DI is common
  - Anterior pituitary deficiencies are less common (20%) GH > Gn deficiency
  - Prolactin can elevate due to stalk effect

Eur J Endocrinol . 2018 Sep;179(3):R151-R163

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5. LANGERHANS CELL HISTIOCYTOSIS

- Diagnosis: Base on histological and immunological criteria
- Chest-Xray and bone survey could be the first line investigations
- MRI finding are not specific to LCH
  - Absence posterior bright spot, stalk thickening, pituitary enlargement.
  - PET/CT scan: used to guide response to therapy or identifying sites of disease more amenable to biopsy than the pituitary gland.
- Treatment: immunosuppressive, chemotherapy or radiotherapy
- New onset DI, in a patient previously considered to be in remission, might be a sign of reactivation of the disease.

Eur J Endocrinol . 2018 Sep;179(3):R151-R163

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6. IMMUNE CHECKPOINT THERAPY RELATED HYPOPHYSITIS

- Ipilimumab (CTLA4 antibody) for malignant melanoma
- Nivolumab (PD1 antibody) and Pembrolizumab (PD1 antibody) for metastasis malignancies
- Higher incidence in males and elderly
- Clinical: headache (common) and cortisol deficiency
  - Visual disturbance and diabetes insipidus is extremely rare
  - Endocrine deficiency: ACTH/TSH -> Gn

Eur J Endocrinol . 2018 Sep;179(3):R151-R163

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6. IMMUNE CHECKPOINT THERAPY RELATED HYPOPHYSITIS

- Immune related adverse effects (irAEs) (hypophysitis, pancreatitis, adrenalitis and thyroiditis)
- Anti-CTLA-4: Hypophysitis
- Anti-PD1: Thyroid dysfuntion
  - 1. Increasing T-cell activity
  - 2. Increasing levels of preexisting autoantibodies
  - 3. Increasing level of inflammatory cytokines
  - 4. Enhance complement-mediated inflammation due to direct bonding to an anti CTLA-4 antibody with CTLA-4 expressed on normal tissue

Postow MA et al. N Engl J Med 2018; 378:158-168

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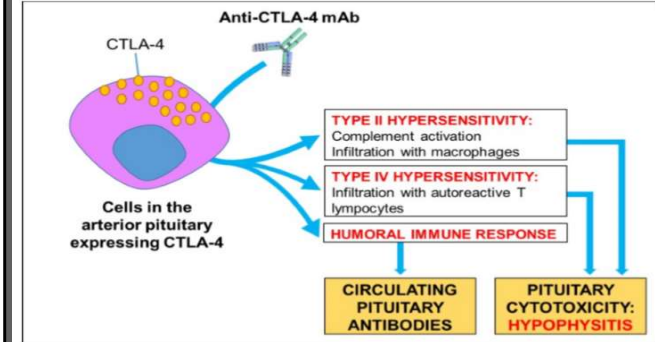

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6. IMMUNE CHECKPOINT THERAPY RELATED HYPOPHYSITIS

- Radiologic: no obvious radiological patterns (primary vs drug induced hypophysitis
- Treatment
  - Mild: hormonal replacement
  - Severe: high dose steroid and discontinuation of the oncology therapy need consideration.
  - After treatment: Adrenal insufficiency is usually no recovery

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4.3 Pituitary - hypophysitis

Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism.

Diagnostic work-up

Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH.

Testing:

Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes

Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes

Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes

G1: Asymptomatic or mild symptoms	Considering holding ICPi until patient is stabilized on replacement hormones Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight) Testosterone or estrogen therapy as needed in those without contraindications Endocrine consultation Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks

Additional considerations

Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies

All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS

Corticosteroid use can cause isolated central adrenal insufficiency

Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions

Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued

For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.

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Characteristics	Primary hypophysitis	Immune checkpoint inhibitor-induced hypophysitis
Etiology	Autoimmune.	Type II and IV hypersensitivity.
Epidemiology	It is more prevalent in young females (female: male ratio ~3:1), apart from the rare IgG4-related form that is more common in older males (female: male ratio ~1:2). The onset of the lymphocytic subtype is strongly associated with late pregnancy and the post-partum period.	The female: male ratio is ~1:4. The mean age at onset is 59 years. The epidemiology is most likely influenced by the underlying malignancy.
Time after the initiating event	Unknown. The median duration of symptoms before clinical presentation is varies according to the anatomic location of the pituitary involvement: Adenohypophysitis (during pregnancy): 4 months; Adenohypophysitis (outside of pregnancy): 12 months; Infundibulo-neurohypophysitis: 3 months; Panhypophysitis: 4 months.	Ipilimumab: median time to onset 9-11 weeks (range 1-35); * Pembrolizumab: median time to onset 16 weeks (range 1-52); * Nivolumab: median time to onset 21-22 weeks (range 6-48); * Ipilimumab + Nivolumab: median time to onset 11-12 weeks (range 3-32). *
Symptoms at presentation	Headache: 47% Adrenal insufficiency: 35% Polydipsia/polyuria: 35% Visual disturbances: 31% Hypothyroidism: 16% Hypogonadism: 20%	Adrenal insufficiency: 72% Headache: 60% Hypothyroidism: 20% Hypogonadism: 15% Visual disturbances: 3% Polydipsia/polyuria: 0.9%

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Characteristics	Primary hypophysitis	Immune checkpoint inhibitor-induced hypophysitis
Pituitary hormone abnormalities	ACTH deficiency: 60% FSH/LH deficiency: 55% TSH deficiency: 52% ADH deficiency: 39% GH decreased: 38% Hyperprolactinemia: 37%	ACTH deficiency: 91% TSH deficiency: 84% FSH/LH deficiency: 83% GH decreased: 43% Hyperprolactinemia: 9% ADH deficiency: 1%
MRI	Abnormal: 98% Normal: 2%	Abnormal: 77% ** Normal: 23%
Histopathology	Marked infiltration of lymphocytes of the pituitary gland, typically accompanied by scattered plasma cells, eosinophils and fibroblasts, and in later disease stages by fibrosis.	T-cell infiltration and IgG-dependent complement fixation and phagocytosis.
Treatment	Usually good response to glucocorticoids.	Good response to glucocorticoids of the symptoms related to sella compression.
Outcome	Variable: from complete recovery, to persistent hypopituitarism.	Pituitary enlargement eventually resolves. TSH and FSH/LH deficiencies often recover, while central adrenal insufficiency persists almost invariably.

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