Hypophysitis

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ENDOCRINOLOGIST

Agenda

- prevalence
- Classification
- Presentation
- Imaging
- Some subtype
- Diagnosis
- management

Definition

- inflammation of the pituitary gland resulting to varying degrees in hypopituitarism and/or symptoms/signs related to sella compression
- Incidence: rare
- accounting for approximately0.24–0.93% of all pituitary disease
- 0.4% of pituitary surgical case
- Primary hypophysitis:1/9 million individuals/year
- constantly increasing with the widespread use of ICIs (immune check point inhibitors)

Classification

- Anatomical classification
- histopathological classification(lymphocytic, granulomatous, xanthomatous, IgG4, and necrotizing)
- etiological classification (primary hypophysitis : or secondary hypophysitis)

Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Jan 1;107(1):10-28.

Presentation

- symptoms related to pituitary deficiencies
- inflammatory process predominantly affects corticotrophs, followed by gonadotrophs and thyrotropes
- mass effect of an enlarged pituitary gland and infundibulum.
- Signs and symptoms depend on the degree of pituitary involvement

Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Jan 1;107(1):10-28.

Table 1 Symptoms at presentation.

Fatigue	52 %
Lethargy	40 %
Headache	38 %
Polyuria + polydypsia	38 %
Nausea	17 %
Emesis	12 %
Visual impairment	17 %
Depressive symptoms	17 %
Weight gain	15 %
Loss of weight	10 %
Loss of libido	15 %
Erectile dysfunction	31 % of men
Amenorrhoea	16 % of women
Adrenal crisis	12 %
Dizziness	10 %
Fever	10 %
Increased sensitivity to cold	8 %
Dry skin	7 %
Body hair loss	5 %

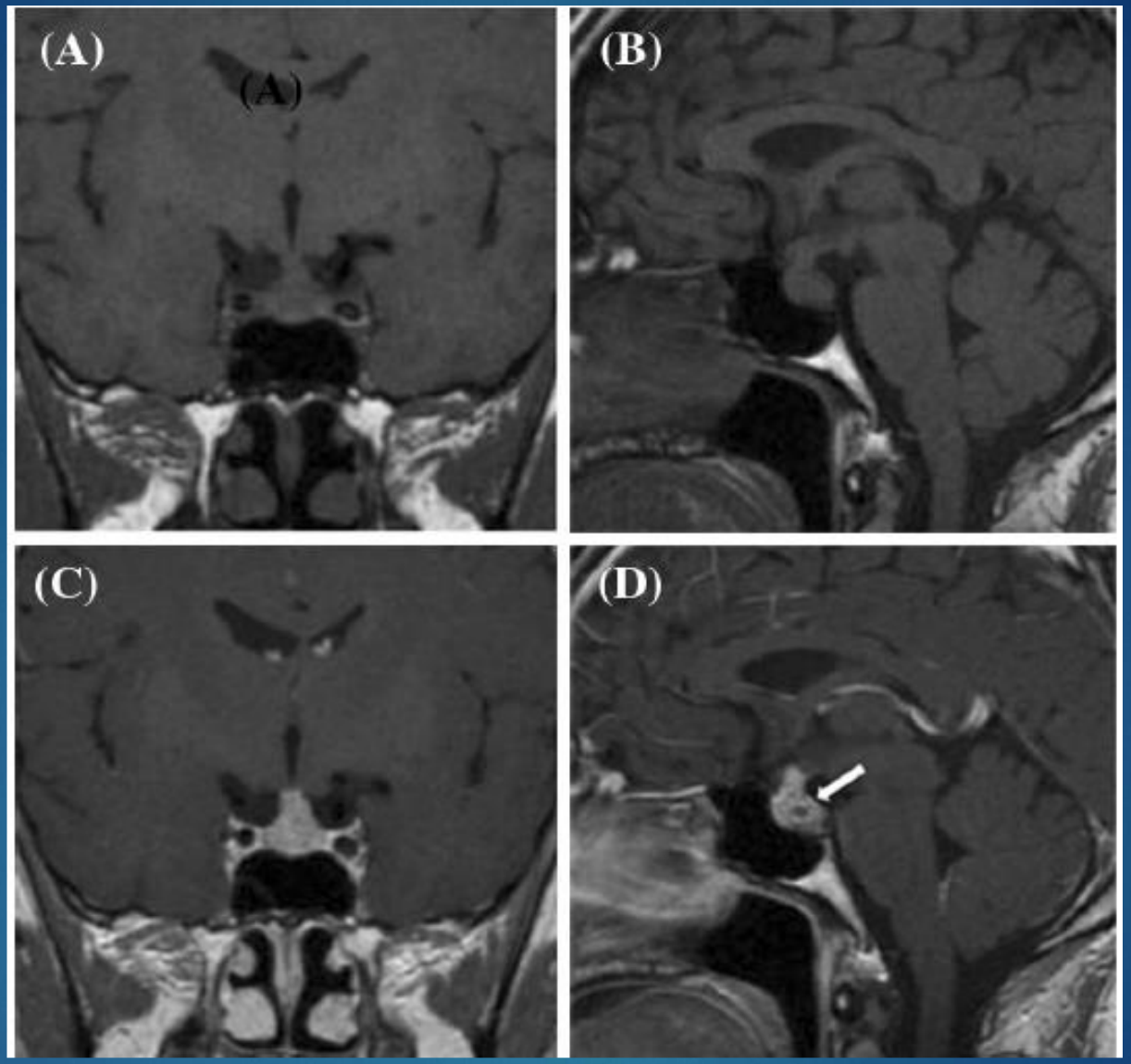
Hormone axis	at diagnosis (n = 60)
Corticotropic	55 %
Thyrotropic	47 %
Gonadotropic	42 %
Somatotropic	10 %
Lactotropic	3 %
Diabetes insipidus	38 %

Amereller F, Küppers AM, Schilbach K, Schopohl J, Störmann S. Clinical characteristics of primary hypophysitis–a single-centre series of 60 cases. Experimental and Clinical Endocrinology & Diabetes. 2021 Mar;129(03):234-40.

Magnetic resonance imaging

- a thickened, nondeviated stalk, mild to moderate symmetric gland enlargement
- Contrast uptake is usually intense, homogeneous less frequently heterogeneous
- loss of posterior pituitary bright spot
- sellar floor is usually intact in hypophysitis
- dural tail sign
- In late disease stages:atrophic pituitary,sellar arachnoidocele or an empty sella

Caranci F, Leone G, Ponsiglione A, Muto M, Tortora F, Muto M, Cirillo S, Brunese L, Cerase A. Imaging findings in hypophysitis: a review. La radiología médica. 2020 Mar;125:319-28



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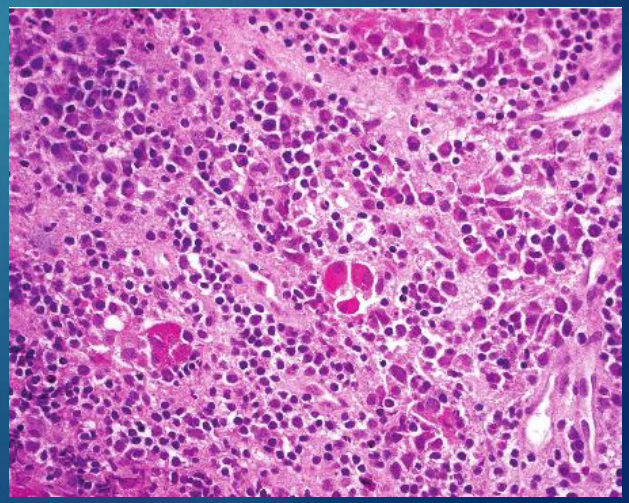
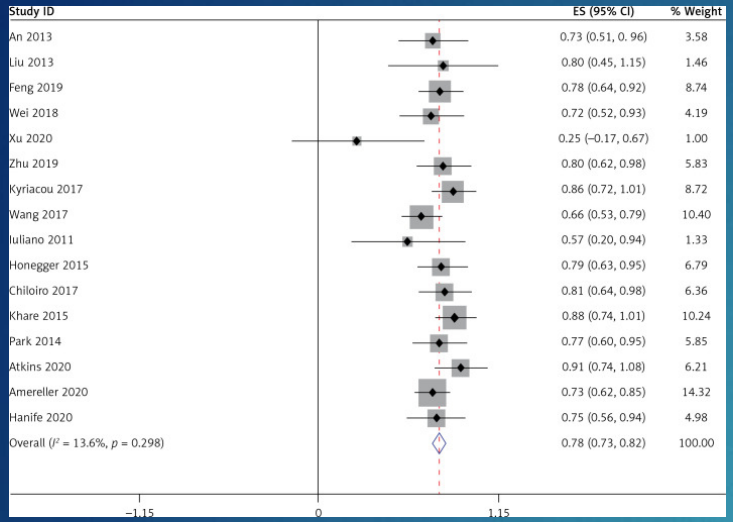
Lymphocytic Hypophysitis

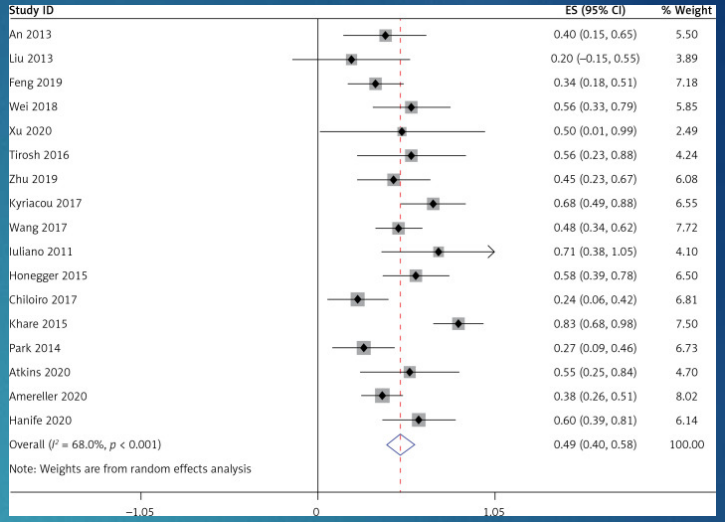
- two thirds of cases of primary hypophysitis forms
- commonly in females
- In women, LHy occurs peripartumin more than half
- Association with a personal or familial history of autoimmune disease
- Predisposing: human leukocyte antigen DQ8 and DR3 alleles



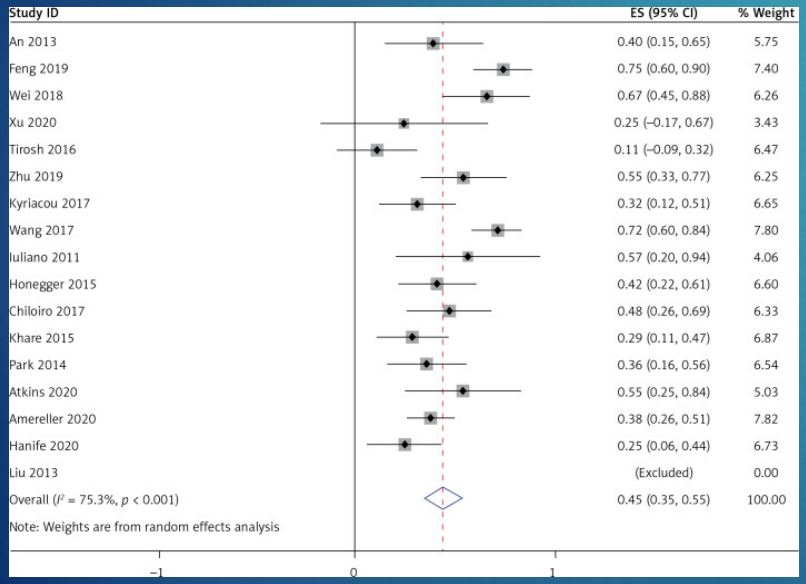
female



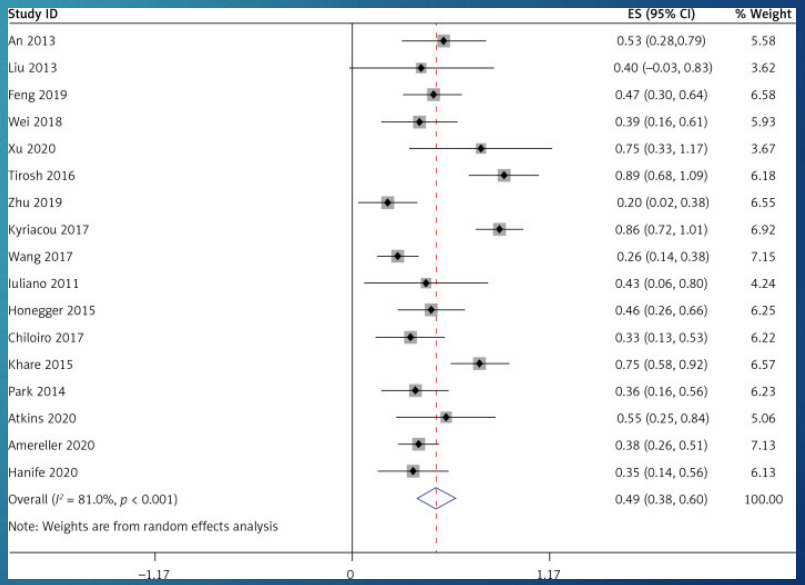
headache



central diabetes insipidus



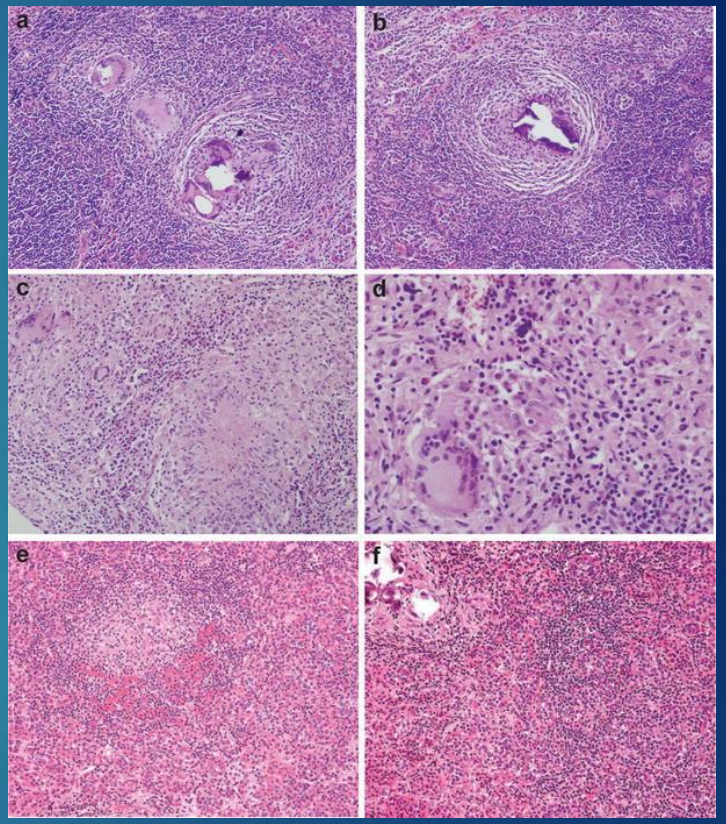
secondary hypoadrenalism



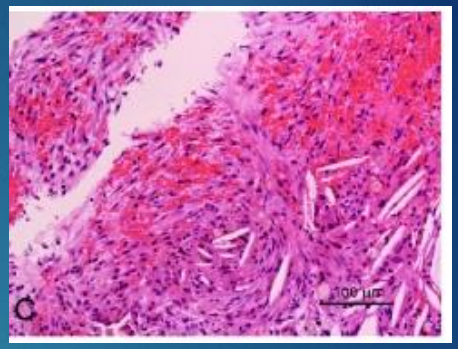
Ju JS, Cui T, Zhao J, Chen JL, Ju HB. Clinical presentation and magnetic resonance imaging characteristics of lymphocytic hypophysitis: a systematic review with meta-analysis. Archives of Medical Science: AMS. 2023;19(4):976.

Granulomatous Hypophysitis

- 20% of primary hypophysitis cases
- a female predominance ,in the fourth decade
- can be associated with autoimmune disorders
- Pathology: multinucleated giant cells and lymphoyctes, numerous histiocytes, some forming granulomas, and variable amounts of fibrosis.
- is usually less GC-responsive compared to Lhy
- Sarcoidosis, Granulomatosis with polyangiitis hypophysitis, Pituitary tuberculoma, LCH



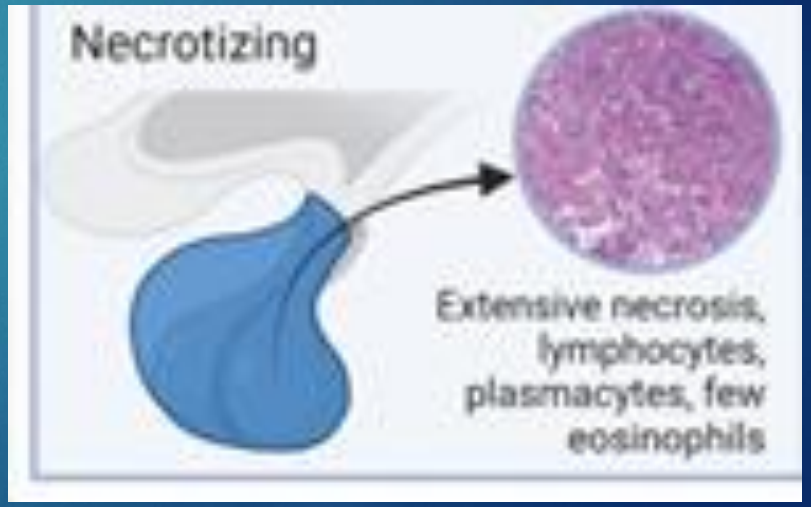
xanthomatous



- Rarest forms of primary hypophysitis
- It is unclear whether XH constitutes a distinct entity
- an infiltration of the pituitary gland by lipid-laden histiocytes and macrophages
- inflammatory condition related to partial rupture of a Rathke's cleft cyst

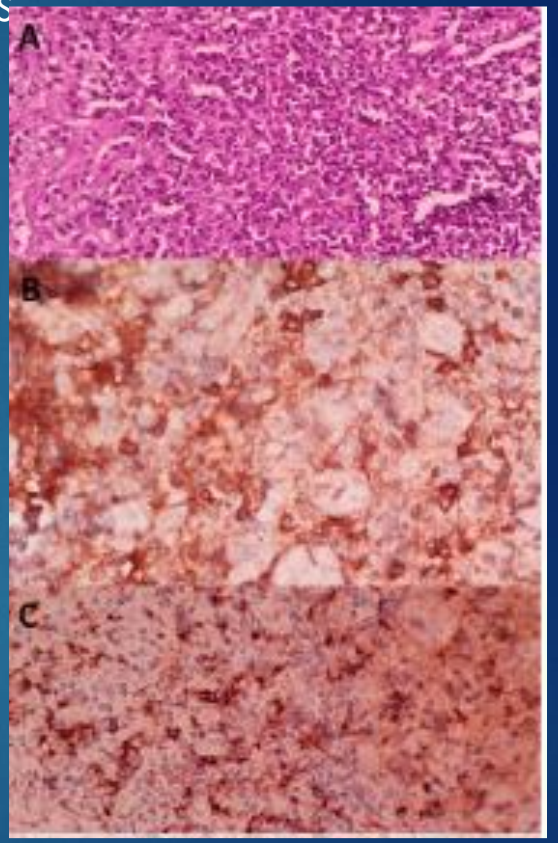
Necrotizing hypophysitis

- very rare
- female>male
- etiology : unknown maybe autoimmune
- MRI: Enlarge gland, poor contrast enhancement
- Apoplexy like appearance



IgG4 hypophysitis

- characterized by a dense infiltration of lymphocytes and IgG4-positive plasmacytes
- incidence : 0.28–1.08/100,000 patients, 30% of all hypophysitis and 4% of all hypopituitarism cases
- male predominance , 7th decade
- may present either as an isolated pituitary lesion (primary hypophysitis) or a multisystemic disease



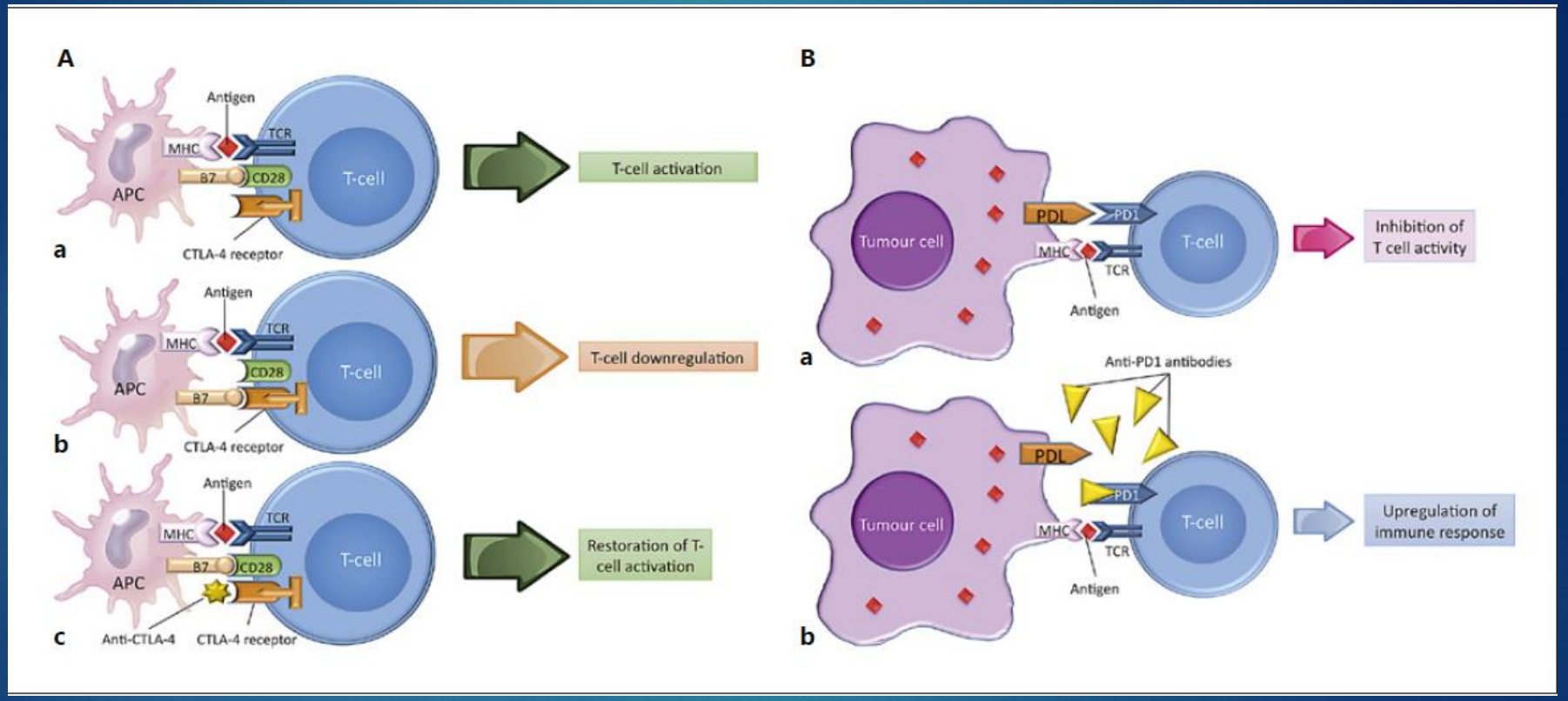
Diagnostic criteria for IGg4 hypophysitis

Criteria	
Histopathology	mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells/high-power field
MRI	sella mass or thickened pituitary stalk
Biopsy	involvement of other organs
Serology	IgG4 > 140 mg/dL
Treatment	clinical and radiological improvement with corticosteroids
Established diagnosis	1 or 2+3 or 2+4+5

IgG4H, IgG4 hypophysitis; MRI, magnetic resonance imaging.

15% to 25% :have normal IgG4 serum levels, mostly women .

Immunotherapy-related Hypophysitis



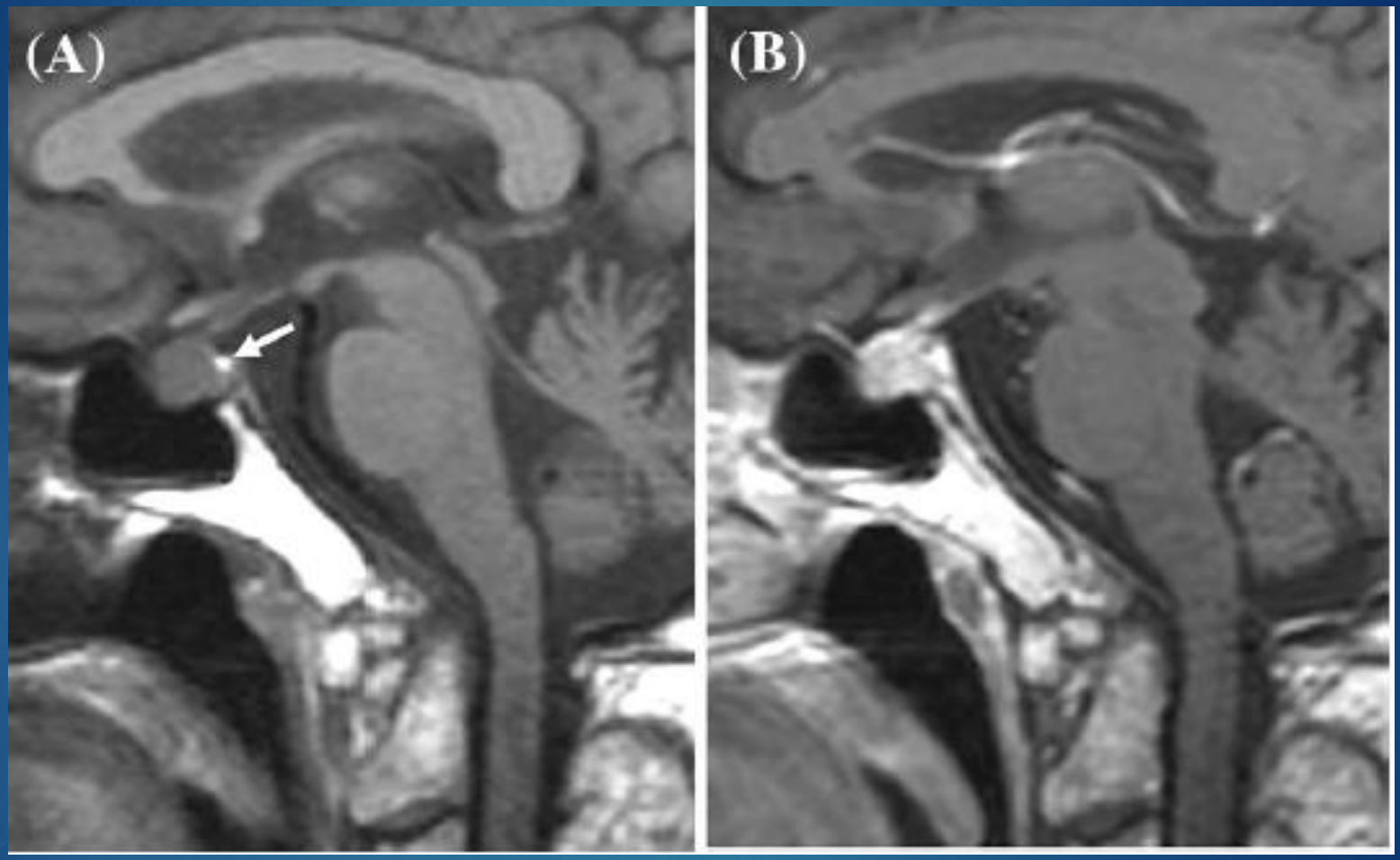
Immunotherapy-related Hypophysitis

- incidence :0.5%-18%, dose-dependent, men and the elderly
- time of onset of hypophysitis for ipilimumab is 9 weeks and 3.3–4.9 months for anti-PD-1
- Mechanism: autoantibodies directed to the pituitary and complement activation (type 2 hypersensitivity reaction) with CTLA-4i.
- CTLA-4 is also expressed by pituitary cells, thus making it a direct target for these drug
- PD-1/PD-L1i compared to CTLA-4i: lower incidence (1%-2%), milder course, development later during treatment, isolated AI, less headaches, and rare MRI changes
- combined anti-CTLA and anti-PD-1/PD-L1 therapies lead to an increased occurrence and earlier disease

Table 1 Longitudinal case cohorts of ipilimumab-induced hypophysitis

	Faje et al. [17]	Min et al. [18]	Albarel et al. [16]	Total
Cohort size (male/female)	154 (99/55)	187 (118/69)	87–131[a] (–)	428–472
Hypophysitis (n, %)	17, 11.0 %	25, 13.3 %	15, 11.4–17.2 %	57, 12.0–13.3 %
Hypophysitis (male/female)	15/2	19/6	10/5	44/13
Hypophysitis mean age (y)	68.2	–	55.5	–
Dosage (3, 10 mg/kg)	13, 4	17, 8	2–4, 11–13[a]	32–34, 23–25
Median time to diagnosis after Ipi initiation (wks)	8.4	9	9.5	–
Radiographic pituitary enlargement	17/17	15/25[b]	12/14[b]	44/56[b]
Visual defects	0/17	0/25	0/15	0/57
Hyponatremia	8/14	14/25	–	22/39
Most common presenting symptoms	HA (14/17), fatigue (10/17)	–	HA (13/15), fatigue (11/15)	HA (27/32), Fatigue (21/32)
Hypopituitarism at diagnosis				
Thyroid	17/17	22/25	13/15	52/56
Adrenal	7/14	22/25	11/15	40/54
Gonadal	15/15	15/20	12/14	42/49
Growth hormone (IGF-1)	1/6	3/7	2/8	6/21
Prolactin (elevated, low)	0/13, 12/13	1/9, 4/9	1/9, 3/9	2/31, 19/31
Diabetes Insipidus	0/17	0/25	0/15	0/57
Resolution of pituitary enlargement	17/17	11/11	12/12	40/40
Hypopituitarism at most recent followup				
Thyroid	13/17[c]	8/25	2/15	23/57
Adrenal	14/17[c]	22/25	13/15	49/57
Gonadal	13/15	8/25	2/15	23/57
Growth hormone (IGF-1)	–	–	1/11	1/11
Prolactin (elevated, low)	–	–	1/11, 1/11	1/11, 1/11

Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary. 2016 Feb;19:82-92.



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ACTH is the most frequent deficit in all checkpoint inhibitors, usually isolated in PD-1/PD-L1i

Pituitary MRI changes can be either subtle or even absent with anti-PD-1 and PD-L1

Number of patients	60
Sex, male, n (%)	37 (61.7)
Age (year), mean ± SD (range)	63.2 ± 11.6 (30–87)
Tumor type, n (%)	
Melanoma	21 (35.0)
Lung	17 (28.3)
Kidney	11 (18.3)
Breast	3 (5.0)
Ovary	2 (3.3)
Gastric	2 (3.3)
Urothelial	1 /1.7)
Colon	1 (1.7)
Oral cavity	1 (1.7)
Hypopharinx	1 (1.7)
Type of ICI, n (%)	
Nivolumab	36 (60.0)
Pembrolizumab	11 (18.3)
Nivolumab + Ipilimumab	4 (6.7)
Nivolumab > Ipilimumab	4 (6.7)
Pembrolizumab > Nivolumab + Ipilimumab	2 (3.3)
Ipilimumab	1 (1.7)
Durvalumab	1 (1.7)
Pembrolizumab > Nivolumab > Nivolumab + Ipilimumab	1 (1.7)
Time to develop IAD after starting ICI therapy (months), median (IQR)	6.0 (4.0–8.0)
Hyponatremia, n (%)	30/44 (68.2)
Eosinophilia, n (%)	15/44 (34.1)
Abnormal pituitary MRI, n (%)	3/43 (7.0)
Other irAEs, n (%)	21 (35.0)
Type of irAE n (%)	
Thyroid dysfunction	16/20 (80.0)
Fulminant type 1 diabetes	1 (5.0)
Other	4 (15.0)

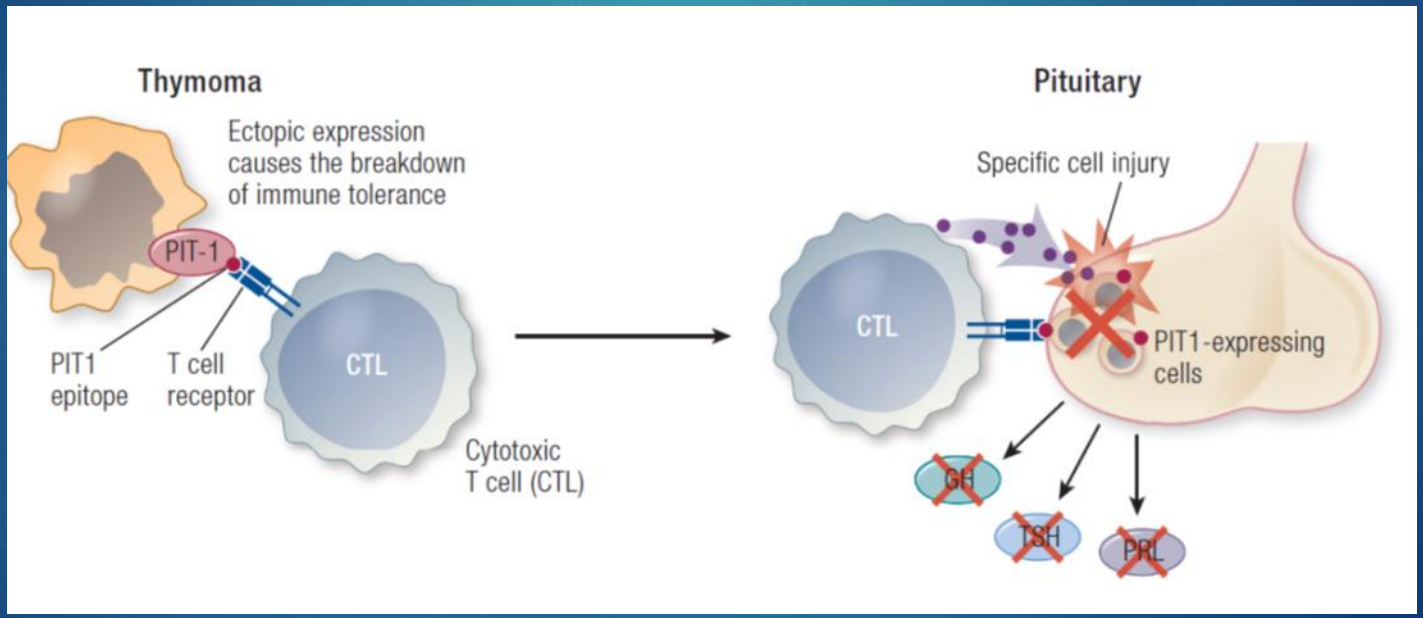
Iglesias P, Sánchez JC, Díez JJ. Isolated ACTH deficiency induced by cancer immunotherapy: a systematic review. Pituitary. 2021 Aug;24(4):630-43.

Follow up

- Patients should be educated about symptoms of AI, (nonspecific)
- clinical assessment and regular adrenal and thyroid monitoring : at least monthly during the first 6 months
- some delayed events : up to 6 to 15 months after immunotherapy cessation

Paraneoplastic Pituitary Autoimmunity

- Tumors that express Pit-1 or proopiomelanocortin/ACTH: lead to production of anti-Pit-1 and anti-ACTH antibodies
- Pit-1 is :differentiation of anterior pituitary cells
- Pit-1 hypophysitis : thymomas and lymphoma



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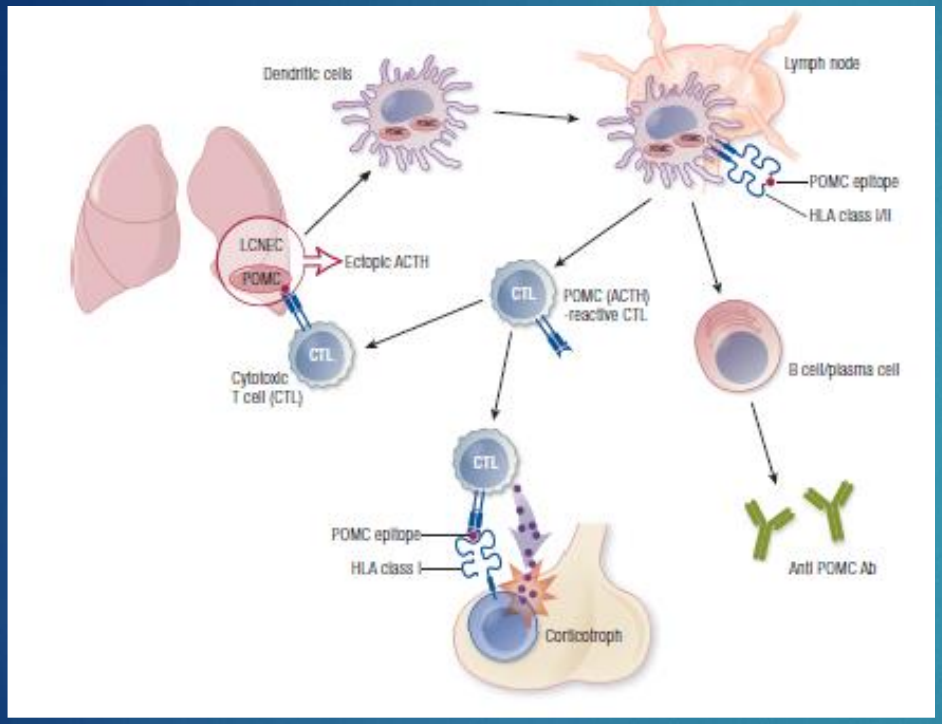
Paraneoplastic Pituitary Autoimmunity



- isolated ACTH deficiency : gastric cancer, lymphoma,ACTH-expressing large cell neuroendocrine carcinoma
- anti-ACTH antibodies :immune destruction of corticotrophs and subsequent AI.

Yamamoto M, Iguchi G, Bando H, Kanie K, Hidaka-Takeno R, Fukuoka H, Takahashi Y. Autoimmune pituitary disease: new concepts with clinical implications. Endocrine reviews. 2020 Apr;41(2):261-72.

Diagnosis

- challenging
- Diagnosis is based on clinical presentation + MRI + laboratory findings
- only a pituitary biopsy can confirm hypophysitis type
- Detailed history and clinical examination are essential, notably for signs of underlying etiology with systemic manifestations

Is a Biopsy Always Necessary to Confirm a Hypophysitis Diagnosis?

- definitive diagnosis
- establishes histopathological type/rules out other etiologies such as neoplasm.
- invasive procedure
- Biopsy is usually considered either when a diagnosis is unclear after initial investigations or when pathology results are needed for treatment

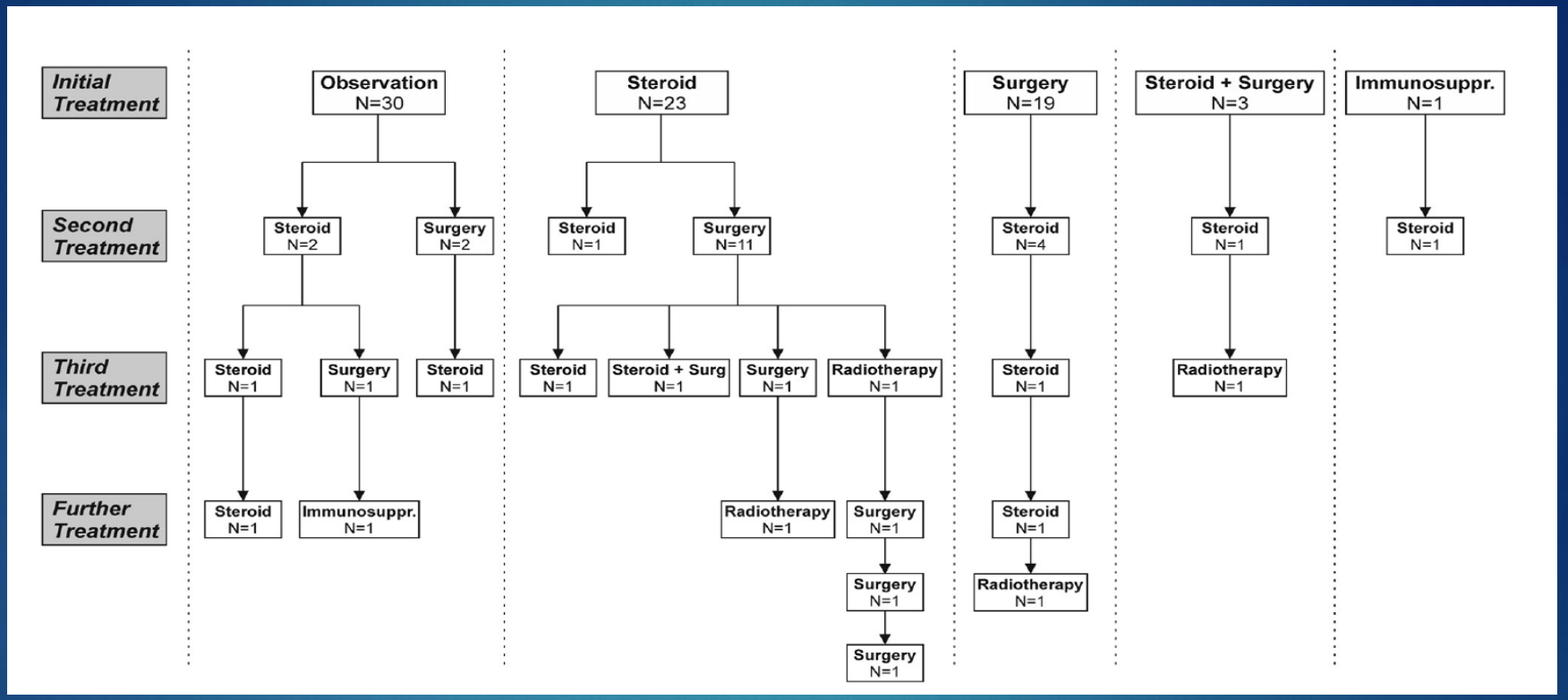
Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Jan 1;107(1):10-28.

How Should Hypophysitis Be Treated?

- treatment should be geared toward the underlying disease etiology and severity.
- acute phase of hypophysitis : may require systemic treatment(glucocorticoid)
- chronic phase:treatment of hypopituitarism

Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Jan 1;107(1):10-28.

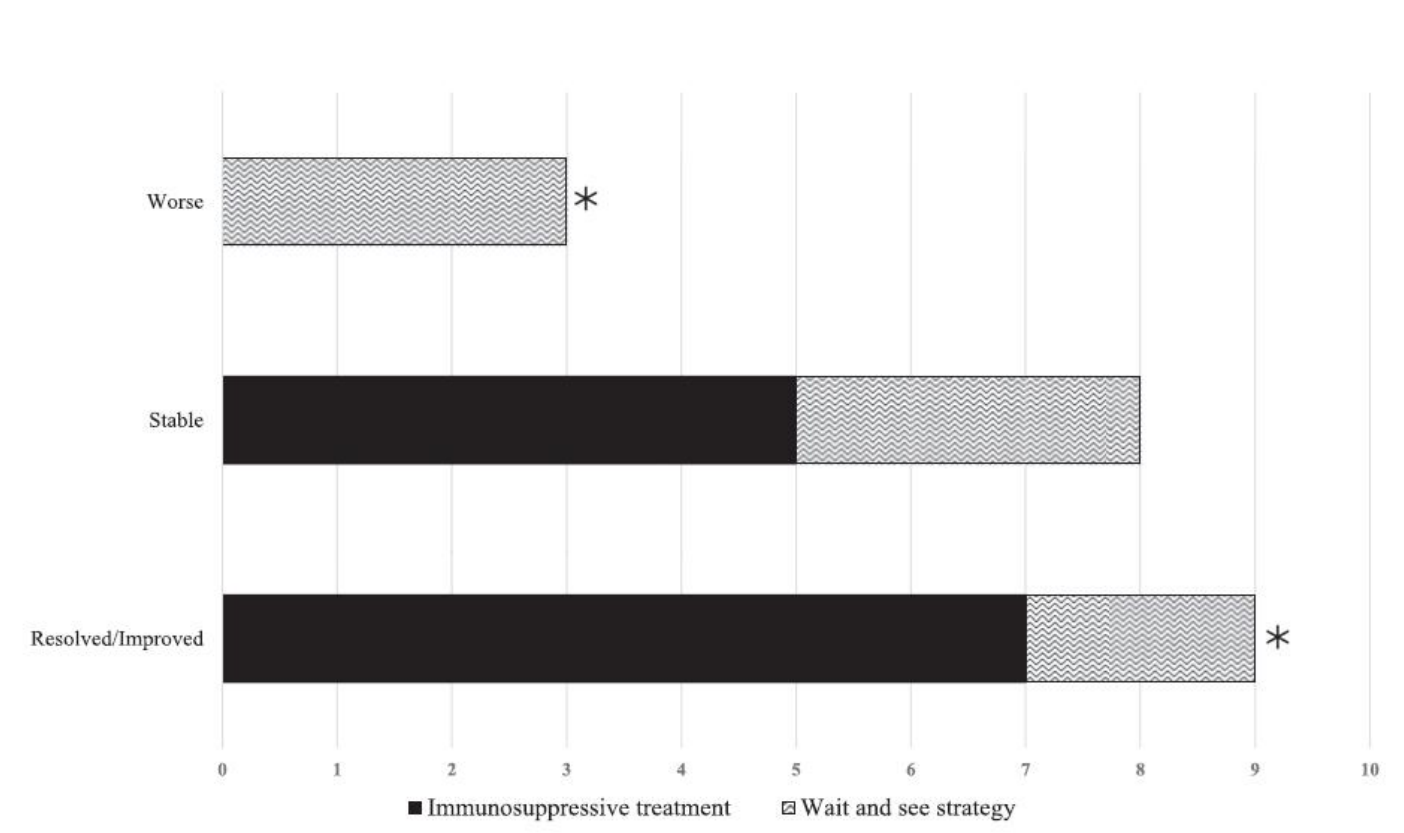
it is unclear whether GC allows for better pituitary function recovery vs simple observation



- In GERMAN cohort(76 patients),for mere observation, regression of space-occupying lesions was observed in 46%, Pituitary function improved in 27% of patients
- the overall failure and recurrence rate of glucocorticoid pulse therapy was 41%. Side-effects of steroids occurred in 63%.

Honegger J, Buchfelder M, Schlaffer S, Droste M, Werner S, Strasburger C, Störmann S, Schopohl J, Kacheva S, Deutschbein T, Stalla G. Treatment of primary hypophysitis in Germany. The Journal of Clinical Endocrinology & Metabolism. 2015 Sep 1;100(9):3460-9.

At the end of a 2-year follow-up, more prednisone-treated patients (58.3%) compared to untreated patients (25%) improved their pituitary function, and 66% of treated vs 25% of untreated had radiographic improvement



Chiloiro S, Tartaglione T, Capoluongo ED, Angelini F, Arena V, Giampietro A, Bianchi A, Zoli A, Pontecorvi A, Colosimo C, De Marinis L. Hypophysitis outcome and factors predicting responsiveness to glucocorticoid therapy: a prospective and double-arm study. The Journal of Clinical Endocrinology & Metabolism. 2018 Oct;103(10):3877-89.

the exact dose, duration, and even indication for GC is still a matter of debate.

- Overall improvement in endocrine function occurs less than reduction in pituitary mass, which can attain closer to a 75% response rate
- primary hypophysitis range widely, between 20 mg/day initial dose to 1 g methylprednisone pulse therapy.

Angelousi A, Alexandraki K, Tsoli M, Kaltsas G, Kassi E. Hypophysitis (including IgG4 and immunotherapy). Neuroendocrinology. 2020 Aug 26;110(9-10):822-35.

In severe disease, visual field and corticotroph axis recovery were significantly higher with i.v. route and very high-dose steroids.

Table 5 Outcomes of glucocorticoid treatment according to baseline severity of cases.

	Mild to moderate		Severe	
	Oral ($n = 51$)	i.v. ($n = 31$)	Oral ($n = 40$)	i.v. ($n = 24$)
Treatment regimen				
Medium dose	6/27 (22.2)	-	9/28 (32.1)[#]	1/23 (4.3)
High dose	20/27 (74.1)[*]	2/29 (6.9)	19/28 (67.9)[#]	2/23 (8.7)
Very high dose	1/27 (3.7)	27/29 (93.1)[*]	0/28 (0)	20/23 (86.9)[#]
Duration of treatment	8 (8–20)	10 (6–12)	12 (6–20)	10 (6–10)
Overall response				
Clinical	22/25 (88)	13/14 (92.9)	25/35 (71.4)	20/22 (90.9)
Hormonal	18/39 (46.2)	13/22 (59.1)	12/26 (46.2)	12/16 (75)
Radiological	23/30 (76.7)	16/27 (59.3)	17/25 (68)	12/20 (60)
Clinical response				
Headache	22/25 (88)	12/13 (92.3)	25/29 (86.2)	20/20 (100)
Visual field deficits	-	-	12/22 (54.5)	11/12 (91.7)[#]
Cranial nerve palsy	-	-	3/6 (50)	7/8 (87.5)
Hormonal response				
Corticotroph	5/17 (29.4)	8/16 (50)	4/15 (26.7)	8/12 (66.7)[#]
Thyrotroph	7/20 (35)	5/12 (41.7)	7/16 (43.8)	5/10 (50)
Gonadotroph	7/21 (66.7)	7/16 (43.8)	9/16 (56.3)	5/10 (50)
Somatotroph	3/7 (42.9)	0/9 (0)	5/8 (62.5)	2/4 (50)
Prolactin normalization	8/12 (66.7)	8/10 (80)	6/7 (85.7)	5/6 (83.3)
Diabetes insipidus recovery	3/16 (18.8)	7/17 (41.2)	6/11 (54.5)	1/5 (20)
Radiological response				
Regression in pituitary mass	15/22 (68.2)	16/20 (80)	21/24 (87.5)	16/20 (80)
Resolution of stalk thickening	19/22 (86.4)	16/25 (64)	12/19 (63.2)	10/16 (62.5)
Need for rescue therapy	17/44 (38.6)	4/31 (12.9)[*]	13/35 (37.1)	6/23 (26.1)

Data are expressed as *n*/N (%) or median (interquartile range).

[*]$P < 0.05$ between oral and i.v. glucocorticoids in mild-moderate cases; [#]$P < 0.05$ between oral and i.v. glucocorticoids in severe cases.

A longer duration oftreatment (>6.5 weeks) was associated with better corticotroph and thyrotroph recovery.

Parameters	Duration of treatment		
	<6.5 weeks ($n = 28$)	6.5–12 weeks ($n = 58$)	(>12 weeks) ($n = 25$)
Overall response (complete/partial)			
Clinical	15/18 (83.3)	35/41 (85.4)	11/15 (73.3)
Hormonal	10/19 (52.6)	25/49 (51.0)	12/18 (66.7)
Radiological	13/22 (59.1)	23/36 (63.9)	15/22 (68.2)
Clinical response			
Headache	14/16 (87.5)	38/41 (92.7)	12/14 (85.7)
Visual defect	3/5 (60)	7/12 (58.3)	1/ 4 (25)
Cranial nerve palsy	2/2 (100)	5/8 (62.5)	0/0 (0)
Hormonal response			
Corticotroph	2/13 (15.4)	13/23 (56.5)*	6/12 (50)
Thyrotroph	1/8 (12.5)	11/21 (52.4)*	8/14 (57.1)$
Gonadotroph	5/12 (41.7)	11/22 (50)	8/16 (50)
Somatotroph	2/8 (25)	3/6 (50)	2/8 (25)
Prolactin normalization	5/11 (45.5)	13/13 (100)*	5/6 (83.3)
Diabetes insipidus recovery	7/9 (77.8)*	0/10 (0)	7/17 (41.2)#
Radiological response			
Regression in pituitary mass	13/19 (68.4)	27/33 (81.8)	13/15 (86.7)
Resolution of stalk thickening	9/13 (69.2)	24/34 (70.6)	13/20 (65)
Need for rescue therapy	8/28 (28.6)	15/56 (26.8)	8/18 (44.4)
Adverse effects	5/15 (33.3)	8/23 (34.8)	4/11 (36.4)

Krishnappa B, Shah R, Memon SS, Diwaker C, Lila AR, Patil VA, Shah NS, Bandgar TR. Glucocorticoid therapy as first-line treatment in primary hypophysitis: a systematic review and individual patient data meta-analysis. Endocrine connections. 2023 Feb 1;12(2).

Very high-dose glucocorticoids(>100mg/day) by i.v. route and cumulative longer duration (>6.5 weeks) lead to better outcomes and could be considered as first-line treatment of severe PAH cases

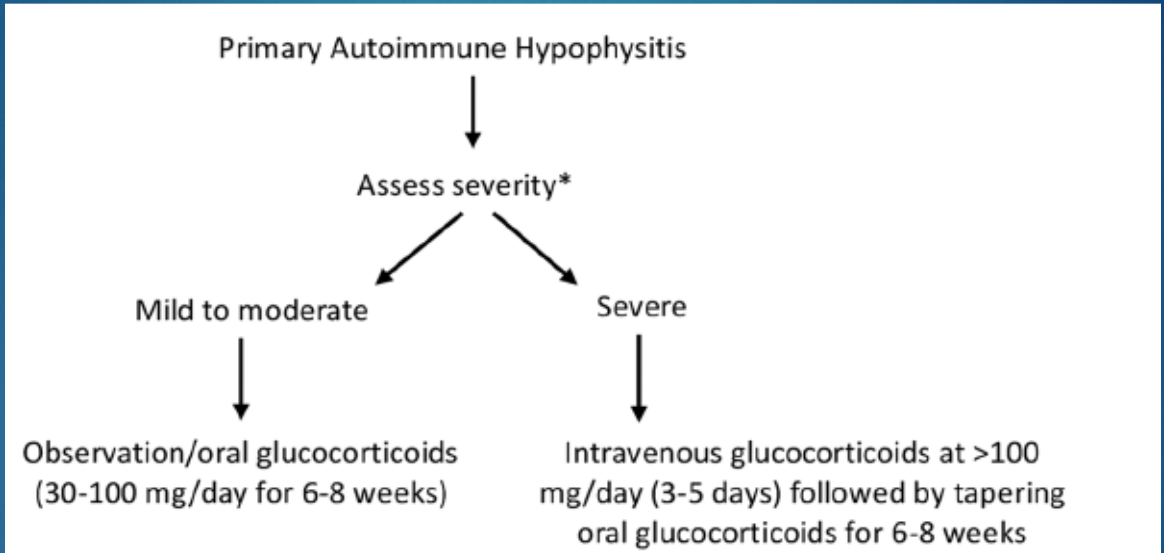


Figure 2
Suggested management algorithm for patients diagnosed with primary autoimmune hypophysitis. *Severe disease: presence of either of the following: visual field deficit, cranial nerve palsy, severe headache, worsening neuro-opthalmologic symptoms/signs. Mild to moderate: absence of severe features.

Krishnappa B, Shah R, Memon SS, Diwaker C, Lila AR, Patil VA, Shah NS, Bandgar TR. Glucocorticoid therapy as first-line treatment in primary hypophysitis: a systematic review and individual patient data meta-analysis. Endocrine connections. 2023 Feb 1;12(2).

Treatment continued

- In patients with mild to moderate headache, mild pituitary dysfunction, no mass effect on optic chiasm, and probable LH, observation may be safely considered
- Initial clinical surveillance can be performed with pituitary MRI at 3 to 6 months.
- if lesions are causing a significant mass :either GC treatment, biopsy, or both should be performed
- periodic reevaluation for pituitary function recovery is needed.
- alert for new symptoms affecting other organs as systemic disorders may manifest later in the course of disease

Immunosuppression therapy

- in GC-refractory cases and as GC-sparing options.
- Azathioprine is the most studied and appears superior for mass reduction than hormonal improvement
- methotrexate and mycophenolate mofetil
- Rituximab, an anti-CD20+, can be used in B-lymphocytes predominant diseases and relapsing IgG4-related disease

Angelousi A, Alexandraki K, Tsoli M, Kaltsas G, Kassi E. Hypophysitis (including IgG4 and immunotherapy). Neuroendocrinology. 2020 Aug 26;110(9-10):822-35.

Surgery

- may be used for decompression of optic chiasm
- GC-resistant cases
- to confirm diagnosis in cases where diagnosis needs clarification.
- patients who underwent surgery had a worse outcome, based on symptoms and endocrine dysfunction

Amereller F, Küppers AM, Schilbach K, Schopohl J, Störmann S. Clinical characteristics of primary hypophysitis–a single-centre series of 60 cases. Experimental and Clinical Endocrinology & Diabetes. 2021 Mar;129(03):234-40.

fractionated radiotherapy and stereotactic radiosurgery

- treatment-resistant and recurrent LHy, radiosurgery is an option to allow
- mass control and discontinuation of immunosuppression

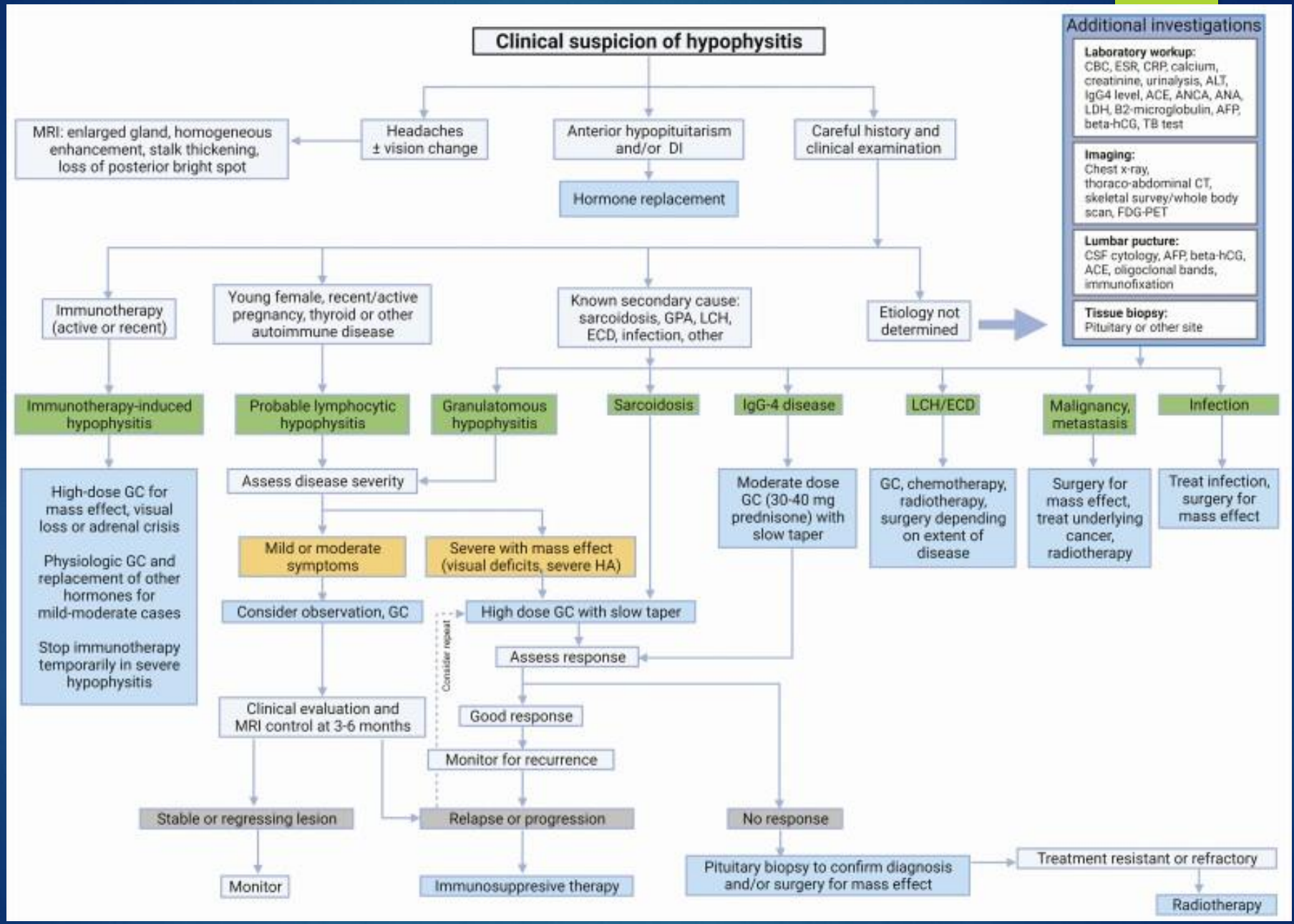
Specific hypophysitis type treatment

- Glucocorticoid therapy is less effective in GH and XH compared to LH
- Igg4 hypophysitis: prednisone, 30 to 40 mg per day, is usually given for 1 to 2 months and then tapered over 2 to 6 months ;rituximab might be a good alternative glucocorticoid resistant cases

Angelousi A, Alexandraki K, Tsoli M, Kaltsas G, Kassi E. Hypophysitis (including IgG4 and immunotherapy). Neuroendocrinology. 2020 Aug 26;110(9-10):822-35.

Treatment of immunotherapy-induced hypophysitis

- Physiologic hormone replacement
- Delaying immunotherapy :in the acute setting until patient is stabilized
- High-dose GCs :in patients with severe symptoms of mass effect, visual loss, or adrenal crisis.
- The adrenal axis rarely recovers in these patients, but gonadal and thyroid may
- Adrenal, gonadal and thyroid axis should be reassessed periodically.



Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. The Journal of Clinical Endocrinology & Metabolism. 2022 Jan 1;107(1):10-28.

Thank you for your attention