Ipofisiti autoimmuni

MALATTIE INFIAMMATORIE DELL'IPOFISI PRIMARIE (linfocitica, granulomatosa, xantomatosa, IgG4-correlata, necrotizzante e forme miste), O SECONDARIE (farmaci tra cui inibitori di check point immunitari, interferone, ribavirina; malattie intracraniche o sistemiche)

A parte la terapia per panipopituitarismo, quale terapia primaria?

Outcome?

Outcome delle ipofisiti e fattori predittori di risposta alla terapia con glucocorticoidi: uno studio prospettico in doppio cieco

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni NON ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario.

Primary autoimmune hypophysitis

is an inflammatory disease of pituitary gland, characterized by an acute phase with infiltration of T and B lymphocytes, plasma cells, and a subsequent progressive glandular fibrosis that typically occurred during the chronic phase of the disease.

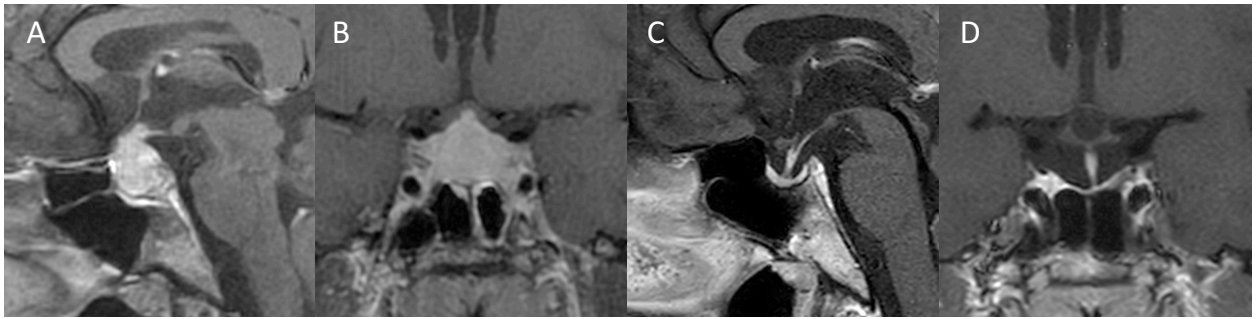
Tang, Brain 2015

The primary autoimmune etiology of hypophysitis is considered an exclusion diagnosis, that may be confirmed only after ruling out secondary causes as granulomatous vasculitis, sarcoidosis, Langerhans cell histiocytosis and tuberculosis, drug-induced

Khare et al. , Pituitary 2015

Primary hypophysitis: natural history and treatment

- ✓ Symptoms of the acute phase of hypophysitis are be due to the sellar compression, as headaches and visual field impairment, hypopituitarism, diabetes insipidus and hyperprolactinemia
- ✓ Primary autoimmune hypophysitis (PAH) evolves in most of untreated cases in a progressive glandular fibrosis, with a secondary empty sella and an irreversible hypopituitarism.
- ✓ PAH outcome, instead, after immunosuppressive treatment hasn't been completely clarified



Secondary empty sella in Patient affected by primary autoimmune hypophysitis.

A,B) Sagittal and coronal post-contrast T1w images show increased volume of the whole pituitary gland and pituitary stalk related to inflammatory changes
C,D) Sagittal and coronal post-contrast T1w images obtained two years later, documentedd an empty sella

- ✓ PAH treatment should be focalized on symptoms, replacement of pituitary hormonal deficits and reduction of inflammatory process.
- ✓ Immunosuppressive PAH treatment should be scheduled according to the acute or chronic phase of the disease.
- ✓ Currently, the debate on the indication, benefits, optimal timing and dosage of glucocorticoids for PAH treatment remains still open.

(1) Su S. et al, Endocrine Journal 2011; (2) Fukuoka H. Endocrinol Metab Clin North Am. 2015; (3) Bellastella G. et al. Pituitary. 2016; (4) Chiloiro S. et al. EJE 2017

Aim

- ✓ to evaluate hypophysitis and pituitary function outcomes;
- ✓ to identify prognostic markers of treatment responsiveness in immunosuppressive glucocorticoid treated patients;
- ✓ to identify markers of disease outcome in conservative managed patients (wait-and-see).

Material and methods

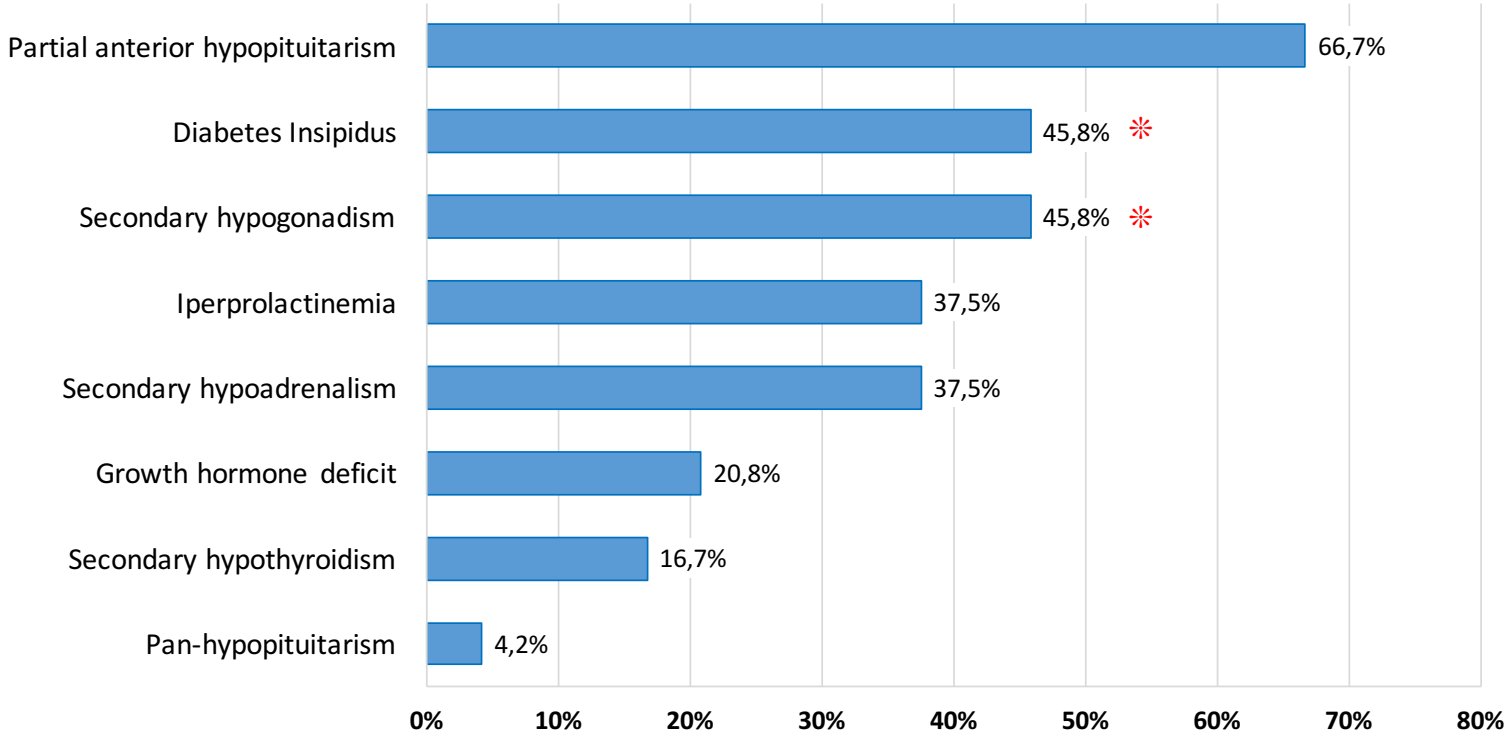
A mono-centric, 2-year prospective, double-arm study (oral prednisone 50 mg daily or conservative managed by observation) was conducted on patients affected by PAH.

Inclusion Criteria
1. Clinical diagnosis of PAH conducted at our Pituitary Unit and 2. positive immunofluorescence determination of serum for anti-pituitary or anti-hypothalamus autoantibodies (respectively APA and AHA), at PAH diagnosis and 3. clinical, endocrine and radiological follow-up (of at least 2-years) conducted at our Hypothalamic and Pituitary Disease Outpatient and Radiological Department.

Key exclusion criteria included pituitary neurosurgery.

Results: Clinical features

20 patients were enrolled. 70% were female

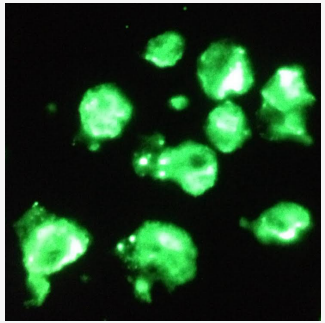


Chiloiro S. et al., JCEM Oct 2018

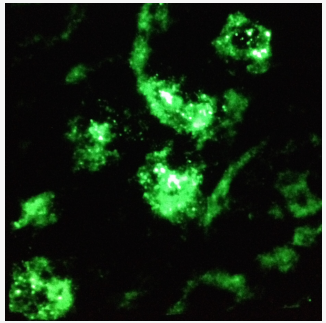
Anti-pituitary (APA) and anti-hypothalamus (AHA) auto-antibodies

An APA o AHA positivity was detected in all cases

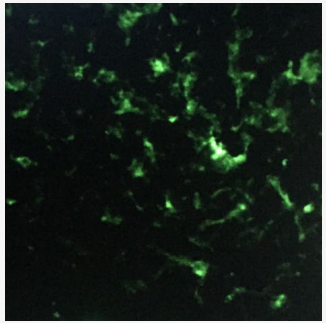
In 11 patients were detected both APAs and AHAs, in 3 patients only APAs and in 6 patients only AHAs.



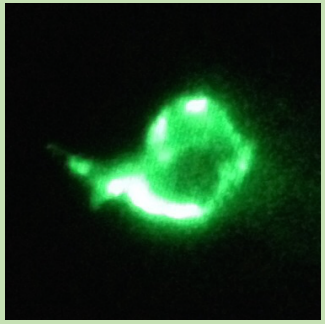
Pituitary anti ANA-Hep-2 (Positive Control)



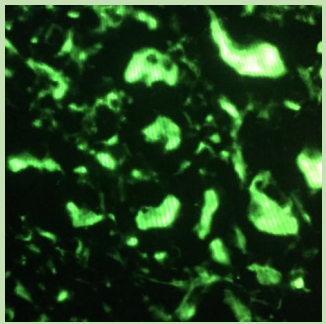
Patient with APA positivity



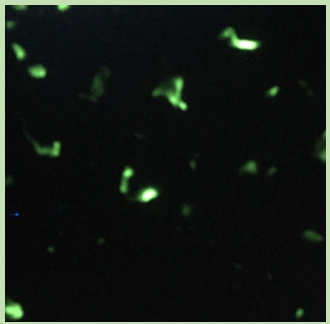
Patient with APA negativity



Hypothalamus anti ANA-Hep-2 (Positive Control)



Patient with AHA positivity



Patient with APA negativity

Indirect immunofluorescence method on monkey hypophysis slides and monkey hypothalamus slides

Serum APA and/or AHA bind to the corresponding antigens present on monkey sections. The antigen-antibody complexes are detected by means of a goat anti-human IgG coniugated with fluorescein isothiocyanate (FITC). IgG FITC was adsorbed with monkey serum to remove non-specific fluorescence. Sera of patients were considered positive for APA and/or AHA starting at a dilution rate of 1:8. Samples were considered positive when a diffuse immunofluorescence pattern showing an intracytoplasmic staining was observed in the majority of fields. In each assay, a positive and negative control was included .

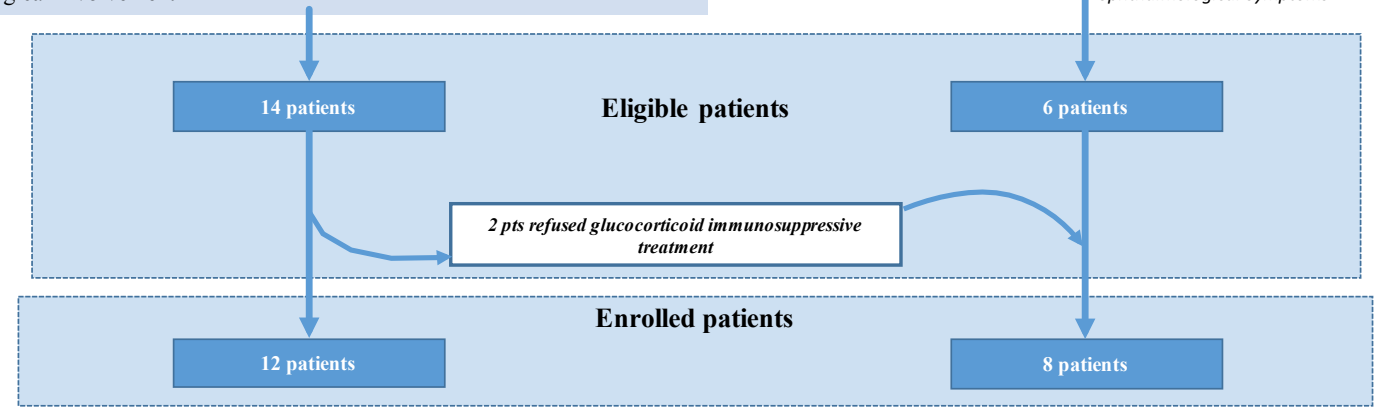
Chiloiro S & Tartaglione T, Neuroendocrinology, 2016

Indication for glucocorticoid immunosuppressive treatment or conservative management follow-up

Indication for glucocorticoid immunosuppressive treatment	Number of patients
Age ≤ 60 years	13
Partial or complete anterior hypopituitarism	6
Diabetes insipidus	0
Partial or complete hypopituitarism + Diabetes insipidus	4
Neurological involvement	2

Indication for conservative management #	Number of patients
Age > 60 years without neurological involvement	3
Major contraindication to glucocorticoid immunosuppressive treatment */§	3

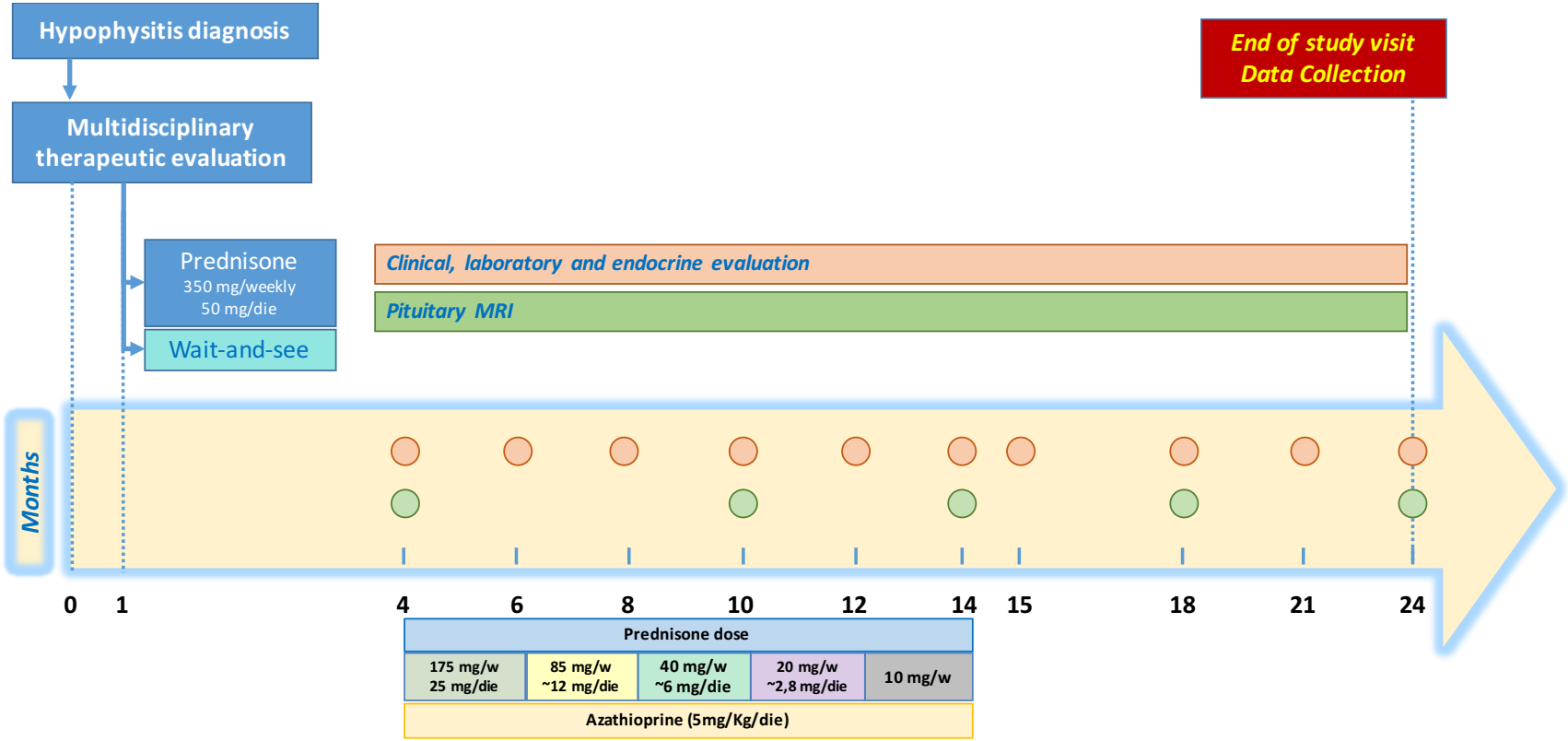
 # None pts was affected by neurological or ophthalmological symptoms



*:2 patients affected by congestive heart failure due to arterial systemic hypertension, without signs and symptoms of PAH-related ophthalmological/neurological involvement
§: a single patient affected by isolated and slight hyper-prolactinemia with a previous history of peptic ulcer disease were conservative managed after a cost-benefit analysis

Chiloiro S. et al., JCEM Oct 2018

Therapeutic protocol



3 of the 12 patients (14% of all cases) started prednisone/azathioprine associative therapy.
At last examination, these patients were still considered not-responding to immunosuppressive treatments.

Baseline

The two treatment groups (oral prednisone 50 mg daily or conservative managed by observation) were similar and none statistically significant differences were detected for all demographic, clinical, immunological and morphological aspects .

Hormonal replacement therapy	
Cortone Acetate/Hydrocortisone	8 patients (median dosage 18.7 mg daily IQR:16.5)
Levothyroxine	2 patients (median dosage: 50 mcg daily IQR: 0)
Acetate desmopressin	6 patients (60 mg table as occurred, median dosage: 60 mg/daily)

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Endocrine outcome

	Immunosuppressive treated pts				Conservative managed pts			
	Baseline	2-years follow-up			Baseline	2-years follow-up		
		Recovered/ Improved	Stable	Worse/ New diagnosis		Recovered/ Improved	Stable	Worse/ New diagnosis
Secondary hypothyroidism	0	Na	Na	0	2	0	2 (66.7%)	1 (33.3%)
Secondary hypogonadism	5	5 (100%)	0	0	2	1 (50%)	1(50%)	0
Secondary hypoadrenalism	5	1 (20%)	4 (80%)	0	1	0	1 (25%)	3 (75%)
GHD	2	2 (100%)	0	0	2	0	2 (100%)	0
Diabetes Insipidus	6	3 (50%)	3 (50%)	0	5	0	5 (100%)	0
Hyper-prolactinemia	2	1 (50%)	1 (50%)	0	3	1 (33.3%)	2 (66.7%)	0

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Hypophysitis prognostic factors

✓ Among patients managed by observation, none clinical, immunological and morphological determinants were identified as able to predict both the morphological and pituitary dysfunction outcome

Patients underwent immunosuppressive glucocorticoid treatment	PROGNOSTIC FACTORS	MR FEATURES OUTCOME	PITUITARY DYSFUNCTION OUTCOME
	APA Positivity	p-value: 0.01 OR: 5 95% CI: 1.4-17.3	p-value: 0.05 OR: 3.3 95% CI: 1.3-8.6
	Secondary hypogonadism	p-value: 0.09 OR: 0.4 95% CI: 0.2 - 1	p-value: 0.03 OR: 0.3 95% CI: 0.09 – 0.9
	Diabetes Insipidus	p-value: 0.01 OR: 0.3 95% CI: 0.1- 1	p-value: 0.002 OR: 0.2 95% CI: 0.02 – 0.9
	Loss of the neuro-pituitary "bright spot" on T1w images	p-value: 0.01 OR: 4 95% CI: 0.7 – 21.8	p-value: 0.002 OR: 0.3 95% CI: 0.1 – 0.9
	Pituitary stalk at optical chiasma >3,9 mm *	p-value: 0.04 OR: 0.3 95% CI: 0.1 - 1	p-value: 0.01 OR: 0.2 95% CI: 0.02 – 0.9
	Infundibulo-neuro-hypophysitis diagnosis	p-value: 0.09 OR: 0.4 95% CI: 0.2 – 1	p-value: 0.03 OR: 0.3 95% CI: 0.1 – 0.9

** ROC Curve: p=0-04; AUC: 0,86 Sensibility: 100% Specificity: 71,4%*

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In conclusion…

- *Hypopituitarism and hypophysitis can improve through glucocorticoid immunosuppressive administration, particularly in patients affected by INH;*
- *The presence of APA and the diagnosis of INH are the main positive prognostic determinants.*
- *Consequently, according to the evaluation of risk/benefit ratio of the glucocorticoid immunosuppressive treatment into a multidisciplinary team, candidate patients should be consequently treated, in order to improve hypophysitis outcome.*

Thank you for the attention

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