Hypophysitis Outcome and Factors Predicting Responsiveness to Glucocorticoid Therapy: A Prospective and Double-Arm Study

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Context: Primary autoimmune hypophysitis (PAH) evolves in most untreated cases in irreversible hypopituitarism. PAH outcome, instead, after immunosuppressive treatment has not been completely clarified.

Objective: To evaluate hypophysitis and pituitary function outcomes.

Design: A prospective, double-arm study with a 2-year follow-up.

Setting: Referral center for pituitary disease.

Patients: Twenty PAH cases.

Interventions: Oral prednisone 50 mg/d or conservative strategy by observation.

Main Outcome Measures: Primary endpoint was the improvement/stabilization/worsening of PAH from baseline to a 2-year visit. Secondary endpoint was the improvement/stabilization/worsening of pituitary function from baseline to a 2-year visit.

Results: Twelve patients (57.1%) were treated with a glucocorticoid-immunosuppressive therapy, and eight patients (42.9%) were observed. At the 2-year visit, PAH improvement/recovery occurred in eight immunosuppressive-treated (66.7%) patients and in two untreated patients (25%). PAH worsened in three untreated patients (37.5%) and was considered stable in four immunosuppressive-treated (33.3%) and three untreated patients (37.5%). Improvement/recovery of pituitary function occurred more frequently in immunosuppressive-treated patients (58.3%) compared with untreated ones (25%; $P = 0.04$). Responsiveness to immunosuppressive treatment is correlated with antipituitary antibody presence ($P = 0.01$), occurrence of diabetes insipidus at PAH diagnosis ($P = 0.01$), absence of the physiological neuropituitary "bright spot" on T1-weighed images ($P = 0.01$), and pituitary stalk at optical chiasm larger than 3.9 mm (area under the curve:

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Abbreviations: ACTH, adrenocorticotropic hormone; AH, adenohypophysis; AHA, antihypothalamus antibody; APA, antipituitary antibody; AUC, area under the curve; GHD, growth hormone deficit; GHRH, growth hormone-releasing hormone; INH, infundibulo-neurohypophysitis; IQR, interquartile range; MR, magnetic resonance; PAH, primary autoimmune hypophysitis; PH, pan-hypophysitis; pMR, pituitary magnetic resonance; T1w, T1 weighed.

0.97, sensibility: 100%, specificity: 100%; $P = 0.04$). On the other hand, we failed to identify factors predicting the outcome, among untreated patients.

Conclusions: Glucocorticoid treatment of hypophysitis improves pituitary secretion and should be encouraged in accordance with the evaluation of endocrine-, immunological-, and morphological-predictive markers. (*J Clin Endocrinol Metab* **103: 3877–3889, 2018**)

Primary autoimmune hypophysitis (PAH) is an auto-immune inflammatory disease characterized by an acute and a subsequent chronic phase. During the acute phase, the pituitary gland appears enlarged, as a result of the infiltration of T and B lymphocytes. On the other hand, a progressive glandular fibrosis typically occurred during the chronic phase of the disease (1). PAHs are characterized by secretory pituitary dysfunction, as a result of a direct and immune-mediated damage of neuroendocrine cells secreting hormones, rather than because of an indirect effect as a result of the pituitary enlargement (2) and the consequent compression or architectural distortion of the pituitary stalk and vessels (3, 4). Consequently, in the early stage of the disease, isolated hormone deficit occurred more frequently (3). In the later/chronic stage of the disease, instead, an extensive and irreversible hypopituitarism is described (5, 6), with a possible evolution in a secondary empty sella syndrome (7). Frequency of pituitary axis deficit ranged widely according to different studies, involving ~80% to 90% of the cases (8, 14). Despite the increased number of reported cases, PAH pathogenesis is still poorly understood. Likewise, the treatment strategies are different and controversial (15). The PAH treatment should be focalized on symptoms, replacement of pituitary hormonal deficits, and reduction of inflammatory process (16). PAH treatment should be scheduled according to the acute or chronic phase of the disease (17). Particularly, in the acute phase, high doses of methylprednisolone, followed by cycles of reduced doses, are suggested for a lower pituitary enlargement and improvement of the pituitary function. Different immunosuppressive agents, as azathioprine, methotrexate, cyclosporine A, and more recently, rituximab and infliximab, have been used and proposed in glucocorticoid-resistant cases or in patients with a major contraindication to glucocorticoid treatment (14, 16). Pituitary neurosurgery, instead, may be considered in patients with severe, persisting, or sudden/rapid progressive neurologic symptoms or morphological signs of compression of nearby structures, as optical chiasm and nerves of the cavernous sinus (14, 16). In PAH chronic phase, hormonal replacement therapy is required for the hypopituitarism. However, PAH outcome after immunosuppressive treatment is not completely clarified: pituitary function and morphological improvements were observed between 15% and 90% of

cases (8–14, 18–20). Treatment outcome seems influenced by pharmacological doses of glucocorticoids, short standing disease, and diagnosis of diabetes insipidus (20–22). Currently, the debate on the indication, benefits, optimal timing, and dosage of glucocorticoids for PAH treatment remains still open (23), and the therapies of hypophysitis present several disputes, without available guidelines or consensus of treatment protocol, according to the rarity of the disease, the lack of prospective studies, and the undefined natural history of the disease (24).

Consequently, we aimed to analyze and compare PAH outcome, among our monocentric series of affected patients, according to treatment choice (high-dose glucocorticoids or clinical observation). At least, we tried to identify prognostic markers of treatment responsiveness in glucocorticoid-treated patients and markers of disease outcome in untreated patients.

Patients and Methods

Study design

A monocentric, 2-year prospective and cross-sectional study was conducted on patients affected by PAH. The study was approved by the Bioethics Committee of the Catholic University of the Sacred Heart.

Patients

Eligible patients were at least 18 years of age and diagnosed with PAH. Among our series of PAH-affected patients (2, 11, 25), were consecutively enrolled patients who satisfied all of the following inclusion criteria:

(1) clinical diagnosis of PAH conducted from November 2008 to April 2015;
(2) immunofluorescence-positive determination of serum for antipituitary or antihypothalamus autoantibodies [respectively, antipituitary antibody (APA) and antihypothalamus antibody (AHA)], at PAH diagnosis;
(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 debulking pituitary neurosurgery.
All patients who were enrolled signed a consent form.

Clinical PAH diagnosis and anatomical classification

Clinical diagnosis of hypophysis was made if the following criteria were satisfied:

(1) occurrence of hypopituitarism and/or hyperprolactinemia and/or diabetes insipidus and/or visual field deficit and/or headache;

(2) exclusion of focal hypothalamic-pituitary lesions/masses (not-secreting and prolactin-secreting pituitary adenomas, craniopharyngioma, germinoma, meningioma, glioma, pituitary apoplexy, pituitary and infundibular metastasis, physiological pituitary hypertrophy, or pituitary hyperplasia as a result of primary hormonal deficits);

(3) identification of the typical PAH findings (4) through a magnetic resonance (MR) as pituitary enlargement in the absence of intraglandular focal lesions/masses and/or pituitary stalk swelling with the absence of the posterior pituitary "bright spot" on T1-weighed (T1w) images;

(4) positivity detection of APA or AHA.

The primary autoimmune etiology of hypophysitis was confirmed after ruling out secondary causes as granulomatous vasculitis, sarcoidosis, Langerhans cell histiocytosis, and tuberculosis, according to diagnostic criteria (8).

PAH cases were anatomically classified (4) through pituitary MR (pMR) images as the following:

(1) adenohypophysitis (AH) in cases with involvement of adeno-pituitary (pituitary enlargement) and without signs of involvement of the neuropituitary gland;

(2) infundibulo-neurohypophysitis (INH) in cases with signs of the infundibulum, pituitary stalk, and neuropituitary involvement (pituitary stalk thickness and absence of the posterior pituitary bright spot on T1w images) without the involvement of the adeno-pituitary;

(3) pan-hypophysitis (PH) in cases of adeno-pituitary, neuropituitary, pituitary stalk, and infundibulum involvement.

Baseline endocrine, immunological, and radiological features

All patients underwent a basal endocrine test of the pituitary function and when indicated, a dynamic test, as adrenocorticotropic hormone (ACTH) stimulation (Synacthen 1 μg eV) and growth hormone-releasing hormone (GHRH; 1 μg/kg) plus arginine (0.5 g/kg, until a maximum dosage of 30 g) tests. Secondary hypothyroidism was diagnosed according to Jostel thyroid-stimulating hormone index (26), whereas diagnosis of secondary hypogonadism was based on low follicle-stimulating hormone and testosterone levels in males, absence of menses in females, and low follicle-stimulating hormone in postmenopausal females. In most cases, clinical history, along with the measurement of 24 hours urinary volume and osmolality during *ad libitum* fluid intake, was an indicator of diabetes insipidus. All patients underwent an APA and AHA determination, according to a previous described protocol (11, 25, 27) (Biosystem, S.A., Barcelona 2010). Moreover, all patients underwent pMR examinations with a 1.5 T MR scanner before and

after the administration of intravenous gadolinium. Pituitary volume, pituitary stalk thickness (both at pituitary insertion and at optical chiasma levels), and the physiological posterior pituitary bright spot on T1w MR images were evaluated in all cases.

Patients' management and data collection

After PAH diagnosis, patients were proposed with an immunosuppressive glucocorticoid treatment (prednisone 50 mg/d) or conservative management (observation), according to the pituitary secretory status, age of patients, and clinical conditions, as summarized in Fig. 1. Glucocorticoid-immunosuppressive treatment was proposed and recommended to (1) young patients (aged <60 years), (2) patients suffering from partial or complete hypopituitarism and diabetes insipidus, and (3) patients who presented with signs and symptoms of ophthalmological and neurologic involvement. A conservative approach was specifically reserved to patients (1) without signs and symptoms of ophthalmological and neurologic involvement, (2) with major contraindication to glucocorticoid-immunosuppressive treatment, and (3) with whom the multidisciplinary clinical evaluation of specific risk/benefit analysis indicated a high risk of adverse events. In the risk/benefit analysis, the potential adverse effects and benefits of the high dose glucocorticoid treatment were evaluated, according to the clinical condition of patients. Hormonal replacement treatment with hydrocortisone, levothyroxine, and desmopressin acetate was prescribed in the case of pituitary deficit. All patients underwent a rheumatology evaluation, both at hypophysitis diagnosis and during follow-up, to evaluate the concomitant autoimmune disorders and manage the immunosuppressive treatments and their potential adverse effects. All patients were clinically followed up and underwent basal endocrine evaluation of pituitary function at 1 and 3 months and then every 3 months from PAH diagnosis, prescription of hormonal
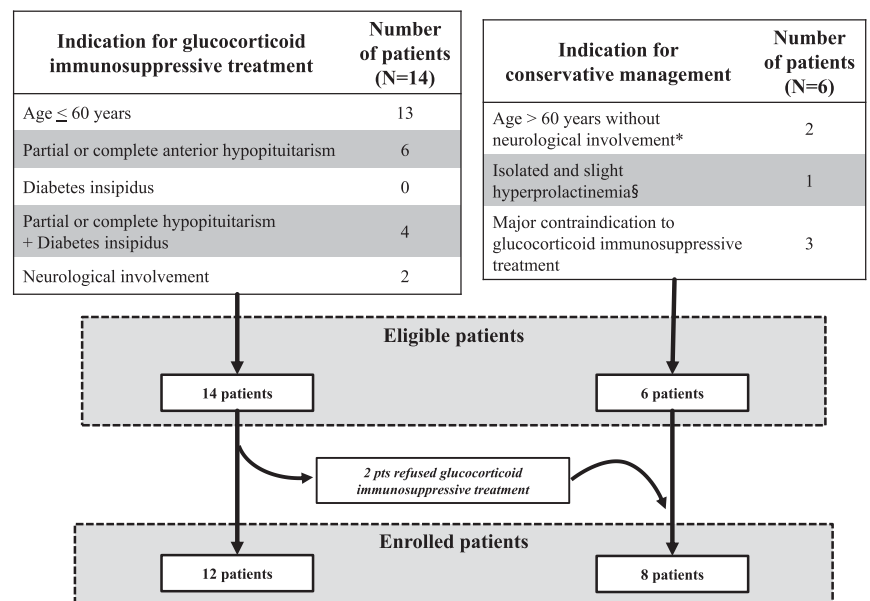
Indication for glucocorticoid immunosuppressive treatment	Number of patients (N=14)
Age ≤ 60 years	13
Partial or complete anterior hypopituitarism	6
Diabetes insipidus	0
Partial or complete hypopituitarism + Diabetes insipidus	4
Neurological involvement	2

Indication for conservative management	Number of patients (N=6)
Age > 60 years without neurological involvement*	2
Isolated and slight hyperprolactinemia§	1
Major contraindication to glucocorticoid immunosuppressive treatment	3

Figure 1. Flow chart summarizing the indication for glucocorticoid-immunosuppressive treatment or conservative management follow-up. *Two patients aged >60 y were affected by congestive heart failure as a result of arterial systemic hypertension, without signs and symptoms of PAH-related ophthalmological/neurologic involvement. §A single patient was affected by isolated and slight hyperprolactinemia with a previous history of peptic ulcer disease and was conservatively managed after a cost-benefit analysis. pts, patients.

replacement, and/or immunosuppressive treatments. A pMR was planned at 3 months from PAH diagnosis and then every 6 months in all patients. An additional pMR was scheduled in cases of worsening of symptoms and/or pituitary function laboratory tests. Prednisone dosage was reduced by 50%, 3 months after the beginning of the treatment, according to the improvement of neuroradiological signs, and then prednisone dosage was reduced by 50% every 2 months (treatment duration: 13 months). On the other hand, in the case of disease progression, prednisone/azathioprine-associative therapy was prescribed (azathioprine dosage: 5 mg/kg/die).

After the completion of the immunosuppressive treatment, endocrine tests were performed at 1 and 3 months and then every 6 months. A pMR was scheduled after 3 and 6 months and then annually. According to the prospective design of the study, clinical and radiological data were collected at the time of PAH diagnosis and at the 2-year follow-up examination.

Endocrine outcome

With the comparison of baseline endocrine features with those collected at the 2-year follow-up examination, endocrine outcome included the following:

(1) resolved in cases of endocrine-deficit resolution, according to the laboratory features or to the withdrawal of the hormonal replacement therapies;
(2) improved in cases of endocrine-deficit improvement, according to laboratory features or to the reduction of the required dosages of hormonal replacement therapies;
(3) stable in cases of endocrine feature stabilization, according to laboratory features or to the maintenance of required dosages of hormonal replacement therapies;
(4) worsened in cases of endocrine-deficit increase, according to laboratory features or to the increase of required dosages of hormonal replacement therapies.

Those patients with a diagnosis of growth hormone deficit (GHD) or secondary hypoadrenalism were retested, respectively, with GHRH plus arginine and ACTH stimulation tests.

Radiological outcome

Baseline and follow-up neuroradiological features

With the comparison of baseline radiological findings with those collected at 2-year follow-up examination, the following radiological outcome was considered:

(1) recovery in the case of reappearance of the physiological posterior pituitary bright spot on T1w MR images and in the case of normalization of pituitary volume and pituitary stalk thickness, according to the value of our reference ranges;
(2) improvement if at least one of the radiological features had improved, and none had worsened;
(3) worsening if at least one of the radiological features had worsened.

Our previous published reference range was established from 74 consecutive age-matched, healthy subjects (2) and was compared with those of other authors (28).

Hypophysitis outcome

The following patients were considered:

(1) cured if all of the endocrine and radiological features had recovered;
(2) improved if at least one of the endocrine or radiological outcome had improved, and none had worsened;
(3) worsened if at least one of the endocrine or radiological outcome had worsened.

Statistical analysis

A descriptive analysis was carried out by median and interquartile ranges (IQRs) for continuous variables and absolute and relative frequencies for qualitative variables. Fisher exact test was applied to compare qualitative variables. The Mann-Whitney and Kruskal-Wallis tests were performed to compare continuous variables. Nonparametric tests were applied because of the non-normal distribution of data. Logistic regression analysis was performed to identify the factors influencing endocrine and PAH outcomes. To obtain the optimal threshold of pituitary volume and pituitary stalk diameter values able to predict the PAH radiological improvement, the receiver operating characteristic analysis was performed. Statistical significance was assumed when $P \leq 0.05$. Data were analyzed using SPSS software, version 22.

Results

Among 29 patients diagnosed for PAH in our Pituitary Unit, 20 patients met the inclusion criteria: two patients were excluded, as they underwent pituitary neurosurgery, two patients had a follow-up shorter than 1 year, and five patients were lost at follow-up. All patients had at least a 2-year follow-up, a single patient reached a 3-year follow-up, and two patients had a 6-year follow-up. Thirteen patients are still in follow-up (median duration: 123 IQR: 99 months).

As shown in Fig. 1, eight patients (42.9%) were managed in a conservatory manner through observation: two patients refused the glucocorticoid treatment, three patients carried a major contraindication to high-dose glucocorticoid treatments (oral candidiasis and unstable diabetes mellitus), and three patients were not treated with an immunosuppressive because of a multidisciplinary medical decision after a risk-benefit analysis (two patients over 60 years were affected by congestive heart failure as a result of arterial systemic hypertension, without signs and symptoms of PAH-related ophthalmological/neurologic involvement, and a single patient was affected by isolated and slight hyperprolactinemia with a previous history of peptic ulcer disease). Twelve patients (57.1% of cases) were treated with prednisone. As a result of radiological worsening, three of the 12 patients (14% of all cases) started prednisone/azathioprine-associative therapy. At last

examination, these patients were still considered unresponsive to immunosuppressive treatments. Regarding patients who had hormonal replacement therapy, eight were treated with hydrocortisone (in six cases in association with prednisone; median dosage 18.7 mg daily; IQR: 16.5), two with Levothyroxine (median dosage: 50 μg daily; IQR: 0), and six with Desmopressin Acetate (60 mg table as occurred, median dosage: 60 mg daily).

Clinical features of the study population, according to the treatment choice, were summarized in Table 1. Particularly, both APAs and AHAs were detected in 11 patients, only APAs in three patients, and only AHAs in six patients.

Endocrine outcome

Endocrine outcome of the entire study population and of the two different treatment groups was summarized in Tables 2 and 3. At the 2-year follow-up examination, observing the group of patients affected by hypopituitarism who underwent the immunosuppressive treatment, four cases showed complete recovery of pituitary function, and improvement of pituitary function was noted in three patients. Particularly, secondary hypogonadism recovered in all patients, GHD in two patients, secondary hypoadrenalism and hyperprolactinemia in one patient, and diabetes insipidus improved in three cases. Worsening of the pituitary function did not occur in any of these patients. After the completion of the immunosuppressive treatment, in no case had the pituitary function worsened.

Among the hypopituitarism-affected patients not treated with immunosuppressive drugs, hyperprolactinemia recovered in a single patient, and secondary hypogonadism improved in another one. On the other hand, worsening of pituitary function resulted in three patients, with the occurrence of secondary hypoadrenalism in all cases and of secondary hypothyroidism in one case. Endocrine outcome is correlated to the treatment choice: improvement/ recovery of pituitary function occurred more frequently in immunosuppressive-treated patients compared with untreated ones (respectively, 58.3% vs 25%; $P = 0.04$), and worsening of pituitary dysfunction occurred only in patients untreated with immunosuppressive therapy (Fig. 2).

Radiological outcome

At the 2-year follow-up examination, among the 18 patients with pituitary enlargement, a volume normalization occurred in six patients, improvement in eight cases, and worsening in four cases.

Pituitary stalk thickness normalized in 11 cases, improved in five cases, and worsened in two cases, among the 18 patients who at diagnosis had a pituitary stalk

thickening. The physiological posterior pituitary bright spot on T1w MRIs did not reappear in any cases. Moreover, a complete recovery of pituitary morphology occurred in two patients, improvement of radiological features was demonstrated in 13 cases, and worsening was in five cases. Among the 12 patients who underwent immunosuppressive treatment, radiological features improved in eight cases and worsened in four cases. Among the eight patients untreated with immunosuppressive drugs, radiological features improved in six cases and worsened in two cases.

Hypophysitis outcome

At the 2-year follow-up examination, among the 12 patients treated with immunosuppressive drugs, eight improved and were consider to respond to the glucocorticoid treatment, and four patients did not improve and were considered resistant to immunosuppressive treatment. Among the eight patients who did not receive immunosuppressive therapy, two cases experienced a spontaneous hypophysitis improvement, three patients were considered stable, and three patients progressively worsened.

Adverse events

The adverse events that occurred in the glucocorticoid-immunosuppressive patients are summarized in Table 4. No serious adverse event occurred. The most frequent adverse event was the increase in weight that was transient and occurred during the first 6 months of treatment. Likewise, metabolic parameters did not significantly change during the treatment period (Table 5). Other adverse events reported were mild hypokalemia, transient psychiatric symptoms, and occurrence of infection (flu syndrome in two patients and cystitis in a single case).

Prognostic factors of hypophysitis outcome

Hypophysitis outcome, according to the treatment choice, is summarized in Table 6. Sex, age at diagnosis, antinuclear antibody, anti-extractable nuclear antigen, and anti-double-stranded DNA autoantibodies did not correlate to endocrine and hypophysitis outcome, both in patients treated and untreated with immunosuppressive therapy. Moreover, among the eight patients who did not undergo the immunosuppressive therapy, we did not identify factors predicting endocrine and hypophysitis outcome. On the other hand, among the 12 patients who underwent immunosuppressive therapy, it was noted that the responsiveness to immunosuppressive treatment, both at univariate and logistic regression analysis (Tables 7 and 8), is correlated with the presence of APA, occurrence of diabetes insipidus at PAH diagnosis, absence of the physiological neuropituitary bright spot on T1w

Table 1. Baseline Clinical Features of Study Population According to Treatment Choice

	Immunosuppressive-Treated Group	Not Immunosuppressive-Treated Group	P Value
Sex			0.5
Male	3 (50%)	3 (50%)	
Female	9 (64.3%)	5 (35.7%)	
Race			0.1
White	11 (91.7%)	5 (62.5%)	
Not White	1 (8.3%)[a]	3 (37.5%)[b]	
Median age at diagnosis (IQR)	42 (29)	36 (31.2)	0.9
BMI, kg/m^2 (IQR)	24.6 (3)	24.5 (4.2)	0.4
APA, n (%)			0.1
Positivity	10 (71.4%)	4 (28.6%)	
Negativity	2 (33.3%)	4 (66.7%)	
AHA, n (%)			0.2
Positivity	9 (52.9%)	8 (47.1%)	
Negativity	3 (100%)	0	
Secondary hypothyroidism, n (%)[c]			0.1
Yes	0	2 (100%)	
No	12 (66.7%)	6 (33.3%)	
Secondary hypogonadism, n (%)[c]			0.3
Yes	5 (71.4%)	2 (28.6%)	
No	7 (53.8%)	6 (46.2%)	
Secondary hypoadrenalism, n (%)[c]			0.2
Yes	5 (83.3%)	1 (16.7%)	
No	7 (50%)	7 (50%)	
GHD, n (%)[c]			0.5
Yes	2 (50%)	2 (50%)	
No	10 (62.5%)	6 (37.5%)	
Diabetes insipidus, n (%)[c]			0.4
Yes	6 (54.5%)	5 (45.5%)	
No	6 (66.7%)	3 (33.3%)	
Hyperprolactinemia, n (%)[c]			0.3
Yes	2 (40%)	3 (60%)	
No	10 (66.7%)	5 (33.3%)	
Anterior hypopituitarism, n (%)[c]			0.5
Yes	6 (54.5%)	5 (45.5%)	
No	6 (66.7%)	3 (33.3%)	
Isolated diabetes insipidus, n (%)[c]			0.2
Yes	0	2 (100%)	
No	12 (66.7%)	6 (33.3%	
Hypopituitarism and diabetes insipidus, n (%)[c]			0.1
Yes	4 (100%)	0	
No	8 (50%)	8 (50%)	
Isolated hyperprolactinemia, n (%)[c]			0.4
Yes	0	1 (100%)	
No	12 (63.2%)	7 (36.8%)	
AH, n (%)	5 (62.5%)	3 (37.5%)	Ref.
PH, n (%)	2 (66.7%)	1 (33.3%)	0.7
INH, n (%)	5 (55.6%)	4 (44.4%)	0.7
Median pituitary volume, mm^3 (IQR)[c]	528.9 (367.6)	617 (470)	0.29
Median pituitary stalk thickness, mm (IQR)[c]			
At optical chiasm	4.5 (2.3)	4 (1.6)	0.37
At pituitary insertion	2.5 (2)	2.2 (0.9)	0.33
Neuropituitary bright spot, n (%)[c]			0.6
Present	5 (62.5%)	3 (37.5%)	
Absent	7 (58.3%)	5 (41.7%)	

Univariate analysis. qualitative variables are reported as absolute value and percent (%). Continuous variables are reported as median ± IQR.

Abbreviations: BMI, body mass index; Ref, reference.

[a]Eritrean ethnicity.

[b]Egyptian, Bengali, and Philippine ethnicity.

[c]Evaluation conducted at PAH diagnosis.

Table 2. Study Population Endocrine Assessment at Baseline and 2-Year Follow-Up

	Baseline	2-Year Follow-Up
Secondary hypothyroidism	2/20	3/20
Jostel index[a]	1.8 (0.8)	1.8 (0.9)
Jostel index[b]	0.94 (−)	1.2 (−)
Secondary hypogonadism	7/20	2/20
Secondary hypoadrenalism	6/20	4/20
Cortisol (μg/dL) after ACTH stimulation[b]	−	Cortisol (microgr/dL) after ACTH stimulation b is 12 (5)
Cortisol (μg/dL) after ACTH stimulation[c]	−	Cortisol (microgr/dL) after ACTH stimulation c is 24 (−)
Cortisol (μg/dL) after ACTH stimulation[d]	−	Cortisol (microgr/dL) after ACTH stimulation d is 11 (7)
GHD	4/20	2/20
GH peak[b]	4.5 (−)	15 (−)[e]
Diabetes insipidus	11/20	8/20
Plasmatic osmolarity, mOsm/kg[b]	304 (9)	293 (7)
Urinary osmolarity, mOsm/kg[b]	40 (23)	254 (345)
Hyperprolactinemia	5/20	3/20
PRL, ng/mL[a]	16 (13.5)	9 (10.25)
PRL, ng/mL[b]	24 (−)	11.4 (−)

Qualitative variables are reported as absolute value and percent (%). Continuous variables are reported as median ± IQR.

Abbreviations: GH, growth hormone; PRL, prolactin.

[a]Value calculated in entire study population.

[b]Value calculated in corresponding pituitary dysfunction-affected patients.

[c]Value referred to the single patient who recovered from secondary hypoadrenalism.

[d]Value referred to the test performed in the three patients with worsening of ACTH–cortisol axis during the follow-up.

[e]Value referred to the median value of GH peak at follow-up GHRH plus arginine test of the two patients who recovered from GHD.

images, and pituitary stalk at optical chiasm larger than 3.9 mm [area under the curve (AUC): 0.97, sensibility: 87.5%, specificity: 100%; P = 0.01]. Likewise, as shown in we Tables 7 and 8, we found that the improvement of pituitary function during follow-up is predicted by the presence of APA, occurrence at PAH diagnosis of secondary hypogonadism, diabetes insipidus, PH and INH anatomical hypophysitis classification, pituitary volume lower than 493 mm^3 (AUC: 0.86, sensibility: 100%, specificity: 71.4%; P = 0.04), pituitary stalk at optical chiasm larger than 3.9 mm (AUC: 0.97, sensibility:

100%, specificity: 100%; P = 0.008), and absence of the physiological posterior pituitary bright spot on T1w MRIs.

Discussion

In this study, we analyzed PAH outcome in our monocentric series of affected patients to identify immunological, clinical, and morphological markers of immunosuppressive treatment responsiveness. We found that the occurrence of diabetes insipidus, the absence of

Table 3. Endocrine Assessment at Baseline and 2-Year Follow-Up According Treatment Choice

	Immunosuppressive-Treated Patients				Conservatively Managed Patients			
		2-Year Follow-Up				2-Year Follow-Up		
	Baseline	Recovered/ Improved	Stable	Worse/New Diagnosis	Baseline	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
Hyperprolactinemia	2	1 (50%)	1 (50%)	0	3	1 (33.3%)	2 (66.7%)	0

Qualitative variables are reported as absolute value and percent (%).

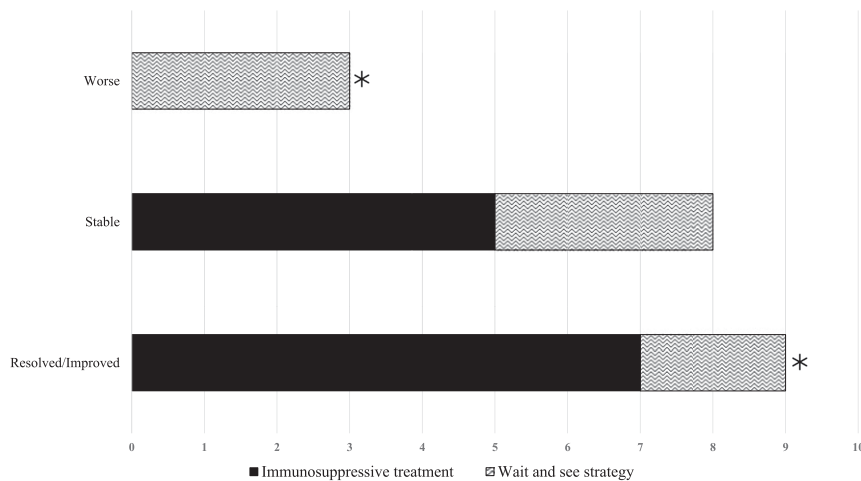Abbreviation: Na, not acceptable.

Figure 2. Histogram representing patients' endocrine outcome according to treatment choice. Bars indicated patients' outcome. Fisher test proved a statistically significant high frequency of worsening of pituitary function among conservatively managed patients compared with immunosuppressive-treated ones (*$P = 0.04$).

the neuropituitary bright spot on T1w MR images, and the pituitary stalk thickness larger than 3.9 mm played an important role in building the positive prognostic markers of hypophysitis and pituitary function improvement at follow-up. Moreover, the occurrence of secondary hypogonadism, as well as pituitary volume lower than 493 mm^3, can predict improvement of pituitary function at follow-up. As previously demonstrated (11), an actual study confirms that secondary hypogonadism and diabetes insipidus, absence of the neuropituitary bright spot, and pituitary stalk thickness larger than 3.9 mm are frequently associated with the diagnosis of PH and INH (Table 9). Likewise, a pituitary volume lower than 493 mm^3 is correlated to the diagnosis of INH ($P = 0.002$). Consequently, our data suggest that both the diagnosis of INH or PH and the indirect clinical and radiological signs of inflammatory involvement of the pituitary stalk and of neuropituitary (such us the pituitary stalk thickness and the absence of the neuropituitary bright spot) can positively predict the hypophysitis outcome. In fact, according to our results, in patients treated with immunosuppressive therapy, INH

and PH are associated with a better prognosis compared with AH cases. However, although autoimmune etiology of primary hypophysitis has been widely described, until now, its pathogenesis is not completely defined, and it is not predictable if INH, PH, and AH differ in disease natural history and treatment responsiveness. In fact, it is possible to speculate that INH, AH, and PH should be supported by different autoantigens, able to trigger the autoimmune inflammation (29). However, several proteins have been suggested as possible PAH antigens, as prohormones and hormones, nuclear and cytoplasmic enzymes, and transcriptional factors, all characterized by a different pituitary cellular expression, involving both the neuroendocrine cells and the T-lymphocytes (30).

Moreover, the different responsiveness to glucocorticoid treatment in cases with inflammatory involvement of pituitary stalk (as INHs and PHs) should be justified by the different vascular system of the pituitary stalk compared with the pituitary glands, which should modify the biodistribution of the drugs (31). In fact, it was previously reported that glucocorticoids almost always improve the swelling of the pituitary and of the pituitary stalk, then inducing a recovery of the anterior hypopituitarism (32).

Moreover, for the first time, our data suggest a prognostic and predictive role of APA on the immunosuppressive treatment responsiveness, reinforcing the hypothesis of the autoimmune inflammation etiology and pathogenesis of PAH (33). APA positivity can consequently suggest an activation of the immune system and an increased sensibility to glucocorticoid treatment. However, until now, APAs have been considered a disease marker rather than causative agent (17). If confirmed on other similar cohorts of patients, use of APA could therefore guide the treatment decisionmaking. Up until now and based on the experience reported in the present manuscript, we can consider APA as a surrogate biomarker of response to treatment.

Prognostic markers of treatment responsiveness were evaluated in our series among patients treated according to the same therapeutic protocol. In fact, the three patients treated with the prednisone/azathioprine-associative therapy were still considered nonresponders to immunosuppressive treatments. Moreover, according to our data, glucocorticoid treatments resulted in usefulness for the improvement of pituitary function and hypophysitis outcome. We found a substantial improvement of gonadal

Table 4. Adverse Events Occurred During Glucocorticoid Treatment

	Patients, n (%)
Transient body weight increase	8 (66.7%)
Transient psychiatric symptoms (anxiety, nervousness)	3 (25%)
Diabetes mellitus	0
Infections	3 (25%; 2 flu syndromes and 1 cystitis)
Mild hypokalemia	3 (25%)

Table 5. Metabolic Assessment in the 12 Patients Treated With Immunosuppressive Glucocorticoid at Baseline and During Follow-Up

	At Immunosuppressive Treatment Start	6 Months Treatment	12 Months Treatment	24 Months Follow-Up
BMI, kg/m^2	24.6 (3.1)	25.1 (2.4)	24.8 (3.6)	24.4 (2.8)
Fasting blood glucose, mg/dL	77 (19)	73 (23.5)	72 (20)	80 (12.5)
HbA$_{1c}$, mmol/mol	36 (2.3)	40 (9)	36 (6)	35 (8)
HDL cholesterol, mg/dL	72 (43)	69 (30.7)	67 (52.5)	64 (23.5)
LDL cholesterol, mg/dL	120.5 (48.2)	119.5 (30.2)	120 (37)	117 (63.5)
Triglycerides, mg/dL	139.5 (118.5)	104 (136)	113 (197.5)	117 (89)

Continuous variables are reported as median ± IQR.

Abbreviations: BMI, body mass index; HbA$_{1c}$, hemoglobin A$_{1c}$; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

function, GHD, and diabetes insipidus, without occurrence of adverse events. Our evidences underline the importance of an etiological-immunosuppressive treatment, particularly in young, fertile-PAH affected patients with a long life expectancy. Hypopituitarism, in fact, is a very serious clinical condition characterized by a high mortality

Table 6. Factors Predicting Hypophysitis Outcome

	Hypophysitis Outcome					
	Patients on Immunosuppressive Treatment (12)			Patients Not on Immunosuppressive Treatment (8)		
	Responder	Nonresponders	P Value	Improved/Stable	Worse	P Value
APA, n (%)			0.03			0.5
Positivity	8 (80%)	2 (20%)		3 (75%)	1 (25%)	
Negativity	0	2 (100%)		2 (50%)	2 (50%)	
AHA, n (%)			0.3			Na
Positivity	5 (55.6%)	4 (44.4%)		5 (62.5%)	3 (37.5%)	
Negativity	3 (100%)	0		0	0	
Secondary hypothyroidism, n (%)[a]			Na			0.4
Yes	0	0		0	2 (100%)	
No	8 (66.7%)	4 (33.3%)		4 (66.7%)	2 (33.3%)	
Secondary hypogonadism, n (%)[a]			0.04			0.7
Yes	5 (100%)	0		1 (50%)	1 (50%)	
No	3 (42.9%)	4 (57.1%)		3 (50%)	3 (50%)	
Secondary hypoadrenalism, n (%)[a]			0.6			0.5
Yes	3 (60%)	2 (40%)		1 (100%)	0	
No	5 (71.4%)	2 (28.6%)		3 (42.9%)	4 (57.1%)	
GHD, n (%)[a]			0.4			0.7
Yes	2 (100%)	0		1 (50%)	1 (50%)	
No	6 (60%)	4 (40%)		3 (50%)	3 (50%)	
Diabetes insipidus, n (%)[a]			0.03			0.5
Yes	6 (100%)	0		2 (40%)	3 (60%)	
No	2 (33.3%)	4 (66.7%)		2 (66.7%)	1 (33.3%)	
Hyperprolactinemia, n (%)[a]			0.4			0.5
Yes	2 (100%)	0		1 (33.3%)	2 (66.7%)	
No	6 (60%)	4 (40%)		3 (60%)	2 (40%)	
AH, n (%)	1 (25%)	4 (75%)	Ref.	3 (100%)	0	0.2
PH, n (%)	2 (100%)	0	0.1	0	1 (100%)	0.6
INH, n (%)	5 (100%)	0	0.02	2 (50%)	2 (50%)	Ref.
Median pituitary volume, mm^3 (IQR)[a]	422 (487)	631 (309)	0.2	537 (508)	644 (1375)	0.5
Median pituitary stalk thickness, mm (IQR)[a]						
At optical chiasm	4.9 (2)	3.3 (0.9)	0.02	3.9 (1.8)	4.1 (1.9)	0.5
At pituitary insertion	2.6 (3.3)	2.1 (2.2)	0.4	2.1 (0.7)	2.8 (1)	0.1
Neuropituitary bright spot, n (%)[a]			0.01			0.2
Present	1 (20%)	4 (80%)		3 (100%)	0	
Absent	7 (100%)	0		2 (40%)	3 (60%)	

Univariate analysis. Qualitative variables are reported as absolute value and percent (%). Continuous variables are reported as median ± IQR.

[a]Evaluation conducted at PAH diagnosis.

Table 7. Factors Predicting Endocrine Outcome

| | Endocrine Outcome | | | | | | | | |
| | Patients on Immunosuppressive Treatment | | | Patients Not on Immunosuppressive Treatment | | | | | |
	Resolved/Improved	Stable	P Value	Resolved/Improved	Stable	Worse	P Value (a)	P Value (b)	P Value (c)
APA, n (%)			0.06				0.7	0.8	0.7
Positivity	7 (70%)	3 (30%)		1 (20%)	2 (40%)	2 (40%)			
Negativity	0	2 (100%)		1 (33.3%)	1 (33.3%)	1 (33.3%)			
AHA positivity, n (%)	5 (41.7%)	7 (58.3%)	Na	2 (25%)	3 (37.5%)	3 (37.5%)	Na	Na	Na
Secondary hypothyroidism, n (%)[a]			Na				0.6	0.8	0.6
Yes	0	0		0	1 (50%)	1 (50%)			
No	7 (58.3%)	5 (41.7%)		2 (33.3%)	2 (33.3%)	2 (33.3%)			
Secondary hypogonadism, n (%)[a]			0.03				0.4	0.5	0.7
Yes	2 (28.6%)	5 (71.4%)		1 (16.7%)	3 (50%)	2 (33.3%)			
No	5 (100%)	0		1 (50%)	0	1 (50%)			
Secondary hypoadrenalism, n (%)[a]			0.3				0.6	0.5	Na
Yes	2 (40%)	3 (60%)		0	1 (100%)	0			
No	5 (71.4%)	2 (28.6%)		2 (28.6%)	2 (28.6%)	3 (42.9%)			
GHD, n (%)[a]			0.3				0.4	0.5	0.7
Yes	2 (100%)	0		1 (50%)	0	1 (50%)			
No	5 (50%)	5 (50%)		1 (16.7%)	3 (50%)	2 (33.3%)			
Diabetes insipidus, n (%)[a]			0.008				0.7	0.2	0.4
Yes	6 (100%)	0		1 (20%)	1 (20%)	3 (60%)			
No	1 (16.7%)	5 (83.3%)		1 (33.3%)	2 (66.7%)	0			
Hyperprolactinemia, n (%)[a]			0.3				0.4	0.2	0.7
Yes	2 (100%)	0		1 (33.3%)	0	2 (66.7%)			
No	5 (50%)	5 (50%)		1 (20%)	3 (60%)	1 (20%)			
AH, n (%)	0	5 (100%)	Ref.	1 (33.3%)	2 (66.7%)	0	Ref.	Ref.	Ref.
PH, n (%)	2 (100%)	0	0.05	0	0	1 (100%)	Na	Na	Na
INH, n (%)	5 (100%)	0	0.004	1 (25%)	1 (25%)	2 (50%)	0.5	0.1	0.5
Median pituitary volume, mm^3 (IQR)[a]	358.9 (467)	705 (300)	0.04	607 (−)	678 (−)	557 (−)	0.6	0.4	0.7
Median pituitary stalk thickness, mm (IQR)[a]									
At optical chiasm	5 (1.4)	3.5 (0.75)	0.005	3.9 (−)	3.8 (−)	4.4 (−)	0.9	0.5	0.7
At pituitary insertion	2.3 (3.9)	2.6 (1.95)	0.5	2.2 (−)	2 (−)	3.1 (−)	0.6	0.1	0.3
Neuropituitary bright spot, n (%)[a]			0.001				0.5	0.1	0.4
Present	0	5 (100%)		1 (33.3%)	2 (66.7%)	0			
Absent	7 (100%)	0		1 (20%)	1 (20%)	3 (60%)			

Univariate analysis. Qualitative variables are reported as absolute value and percent (%). Continuous variables are reported as median ± IQR. P value (a), compared the group of patients with resolved pituitary dysfunction with patients with stable endocrine assessment; P value (b), compared the group of patients with stable endocrine assessment with those with worsened pituitary endocrine function; P value (c), compared the group of patients with improved/resolved endocrine assessment with those with worsened pituitary endocrine function.

[a]Evaluation conducted at PAH diagnosis.

risk and consequently, required an expensive hormonal replacement therapy (34).

In our group of untreated patients, a spontaneous recovery of hypophysitis and pituitary function occurred rarely: in most of cases, hypopituitarism did not change or worsened during the follow-up stage. However, our data did not allow us to identify a prognostic marker of hypophysitis outcome in patients who were not treated with glucocorticoids.

In previous studies, among patients who underwent an immunosuppressive treatment, pituitary secretion improvement was proven between 15% and 41% and radiological improvement between 36% and 89% of cases (14, 19, 20, 35). Among patients who did not undergo an immunosuppressive treatment, instead, the improvement of pituitary function was reported in 33% (8) and the spontaneous radiological improvement in 72.7% of cases (19). This variability is justified by sample size, study population selection bias, different disease stage, treatment choice and drug dosage, and definition of the treatment responsiveness and of the outcome. Moreover, most of these studies were retrospectively designed. The positive outcome proven in our series can be explained by an early hypophysitis diagnosis and initiation of immunosuppressive treatment and the availability of a tertiary referral center with a medical team devoted to pituitary disease.

Table 8.   Factors Predicting Hypophysitis and Endocrine Outcome

	Hypophysitis Worsening at Follow-Up	Worsening of Pituitary Function at Follow-Up
APA positivity[a]	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[a]	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[a]	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
Absence of neuropituitary bright spot	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 volume <493 mm^{3a}	P value: 0.09 OR: 2.3 95% CI: 1–5.5	P value: 0.03 OR: 3.5 95% CI: 1.1–11.3
Pituitary stalk at optical chiasm >3.9 mm[a]	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
PH diagnosis	P value: 0.8 OR: 0.2 95% CI: 0.03–1.2	P value: 0.01 OR: Na 95% CI: Na
INH 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

Logistic regression.

[a]Evaluation conducted at PAH diagnosis.

According to previous literature, the role of surgery in treatment of hypophysitis is limited to selected cases, such as those with diagnosis in doubt or those with a rapid/sudden progression of neurologic symptoms (20). In fact, although some authors suggested that pituitary neurosurgery may improve PAH morphologically (19), the same does not allow the improvement of pituitary function. Immunosuppressive treatment with pharmacological doses of glucocorticoid is considered ideal compared with pituitary surgery and conservative management (clinical observation) for restoring pituitary secretory function (8, 20). Likewise, in our two patients who underwent debulking pituitary neurosurgery for the

worsening of the neurologic symptom (11), we did not obtain a pituitary secretory improvement. However, according to the different treatment and to the well-defined postsurgery pituitary region anatomical modifications, we decided to exclude these two patients in the current study.

In our series, PAH recurrence did not take place. However, data of hypophysitis recurrence after immunosuppressive treatment are variable in previous reports, ranging from 18% to 40% (14, 19, 20). These data can be influenced by the glucocorticoids dosage and treatment period. In our series, duration of glucocorticoid treatment was at least 13 months, according to a slow

Table 9.   Prognostic Factors Predicting Hypophysitis and Endocrine Outcome, According to Anatomical Hypophysitis Classification

	AH	PH	INH	P value AH vs PH	P value AH vs INH	P value PH vs INH
Secondary hypogonadism[a]	0	1 (16.7%)	5 (83.3%)	0.3	0.01	0.3
Diabetes insipidus[a]	0	3 (27.3%)	8 (72.7%)	0.08	<0.001	Na
Absence of neuropituitary bright spot[a]	0	3 (25%)	9 (75%)	0.08	<0.001	Na
Pituitary stalk at optical chiasma >3.9 mm[a]	0	2 (22.2%)	7 (77.8%)	0.02	<0.001	0.3
Pituitary volume <493 mm^{3a}	0	0	6 (100%)	Na	0.002	0.002

Univariate analysis. Qualitative variables are reported as absolute value and percent (%).

[a]Evaluation conducted at PAH diagnosis.

reduction of glucocorticoid pharmacological dosage. In fact, treatment with glucocorticoid can reduce the inflammatory edema in an early phase of the disease and prevent the development of a chronic inflammation and related fibrotic process in a later disease stage (36).

The main limitations of our paper are the following: (1) the small size of the study population, (2) the low frequency of the histopathological diagnosis of PAH, and (3) the nonrandomized study design. Our study cohort was chosen with the application of a very strict inclusion criteria, to select a homogeneous study group of patients diagnosed, treated, and followed up according to a univocal protocol, by a unique medical team devoted to pituitary disease (namely, the Pituitary Board). However, our study cohort results are very similar to those investigated by other research groups, also reflecting the reported PAH prevalence.

Moreover, despite the nonrandomized study design, our paper represents a real-life scenario in which PAHs were treated with immunosuppressive therapy according to pituitary secretory status and the age of the patients, clinical condition, and preference. Nevertheless, our study was conducted in a cross-sectional and prospective view in the two groups of patients classified as immunosuppressive treated and untreated without differences of baseline disease aspects.

Although our data should be confirmed on larger patient series, our actual evidences suggest that hypopituitarism and hypophysitis can improve through glucocorticoid immunosuppressive administration, particularly in patients affected by INH and PH. Consequently, according to the evaluation of the risk/benefit ratio of glucocorticoid-immunosuppressive treatment, candidate patients should be consequently treated, also according to the endocrine, immunological, and morphological potential biomarker of treatment responsiveness.

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