Predictive Role of the Immunostaining Pattern of Immunofluorescence and the Titers of Antipituitary Antibodies at Presentation for the Occurrence of Autoimmune Hypopituitarism in Patients with Autoimmune Polyendocrine Syndromes over a Five-Year Follow-Up

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Context: Antipituitary antibodies (APA) are frequently present in patients with autoimmune polyendocrine syndrome (APS).

Design: The aim was to evaluate the predictive value of APA for the occurrence of hypopituitarism. A total of 149 APA-positive and 50 APA-negative patients with APS and normal pituitary function were longitudinally studied for 5 yr.

Methods: APA, by indirect immunofluorescence, and anterior pituitary function were assessed yearly in all patients. The risk for developing autoimmune pituitary dysfunction was calculated using survival and multivariate analysis.

Results: Hypopituitarism occurred in 28 of 149 (18.8%) APA-positive patients but in none of the 50 APA-negative patients. The immunostaining pattern in APA-positive patients involved either isolated pituitary cells [type 1 pattern; n = 99 (66.4%)] or all pituitary cells [type 2 pattern; n = 50 (33.6%)]. All patients developing pituitary dysfunction throughout the study span had a type 1 pattern. Kaplan-Meier curves for cumulative survival showed a significantly higher rate for developing hypopituitarism in relation to positive APA tests (P < 0.005), pattern of immunostaining (P < 0.0001), and APA titers (P < 0.000001). Cox regression analysis in APA-positive patients with a type 1 pattern demonstrated a significantly (P < 0.0001) higher risk for the onset of hypopituitarism in relation to increasing titers of APA.

Conclusions: APA measurement by immunofluorescence may help to predict the occurrence of hypopituitarism but only when considering the immunostaining pattern and their titers. Combined evaluation of these parameters allows identifying patients at higher risk for pituitary autoimmune dysfunction, thus requiring a strict pituitary surveillance to disclose a preclinical phase of hypopituitarism and possibly interrupt therapeutically the progression to clinically overt disease. (J Clin Endocrinol Metab 95: 0000–0000, 2010)

Patients affected by autoimmune polyendocrine syndromes (APS) are the best source of organ-specific antibodies (1). Usually these antibodies are detected in more than 90% of affected patients at the onset of the clinical phase, but sometimes also in the preclinical phase of the autoimmune disease (2–5). Autoantibodies are generally considered good predictive markers of clinically overt disease (6–11). Antipituitary antibodies (APA) may

Abbreviations: APA, Antipituitary antibodies; APS, autoimmune polyendocrine syndromes; FT3, free T3; FT4, free T4; GHD, GH deficiency; PRL, prolactin.
be detected in patients with isolated endocrine diseases or with APS. However, their role in the development of pituitary failure remains to be clarified (12, 13). Several studies demonstrated no relationship between the presence of APA in serum and the occurrence of anterior pituitary dysfunction in patients with autoimmune endocrine diseases (14–18). These reports indicated that most patients showing positive tests for APA display normal pituitary function, whereas only a few of them present with functional pituitary alterations suggestive of lymphocytic hypophysitis (19–21). APA-positive sera may produce different immunostaining profiles. A diffuse immunostaining pattern involving virtually all pituitary cells is observed with some APA-positive sera, whereas others produce focal immunostain areas involving only a proportion of pituitary cells (18, 22). The issue of whether the positivity for APA, as detected by immunofluorescence, should be considered a diagnostic marker of lymphocytic hypophysitis and a predictor of impending pituitary failure remains controversial. The different immunostaining patterns produced by APA-positive sera could be one of the factors responsible for the discrepant results reported in the literature. The occurrence of hypopituitarism in patients with positive tests for APA in relation to the immunostaining pattern produced by their sera and titer of APA was not investigated previously.

The aim of this longitudinal 5-yr study was to investigate changes in the pituitary function and the titer of APA in patients with positive tests for APA and normal pituitary function at booking and to relate these changes to the specific immunostaining pattern produced by their sera.

Patients and Methods

Patients
From 2000 to 2007, a screening for APA was performed in a large cohort of 700 patients with APS in our immunoendocrinology laboratory of Naples on the account of the Italian Autoimmune Hypophysitis Network Study. All units involved in the study contributed to the recruitment of patients. APA were measured by an immunofluorescence method. All 149 patients with APA-positive results (41 males, 108 females; age range, 20–45 yr) and 50 of the remaining APA-negative patients (10 males, 40 females; age range, 25–42 yr) gave their written informed consent to be enrolled into this longitudinal study, which was approved by the local institutional review board (Review Board of Department of Clinical and Experimental Medicine and Surgery 'F. Magrassi, A. Lanzara,’ Second University of Naples).

### TABLE 1. Clinical features of patients with APS in relation to the presence or absence of APA

<table>
<thead>
<tr>
<th></th>
<th>APA-positive (n = 149)</th>
<th>APA-negative (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (males/females)</td>
<td>41/108</td>
<td>10/40</td>
</tr>
<tr>
<td>Mean age ± SD (yr)</td>
<td>32.05 ± 5.74</td>
<td>32.76 ± 5.51</td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>20–45</td>
<td>25–42</td>
</tr>
<tr>
<td>APS type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>136</td>
<td>47</td>
</tr>
<tr>
<td>Type 4</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Coexisting autoimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diseases in APS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>103</td>
<td>36</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Autoimmune atrophic</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>gastritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

At booking, all of the 149 APA-positive and 50 APA-negative patients had normal anterior pituitary function, including normal prolactin (PRL) levels. The clinical features of patients enrolled in the study are illustrated in Table 1. According to the revised classification of APS (1, 23), 136 APA-positive patients had a type 3 APS and 13 had a type 4. Among the 50 APA-negative patients, 47 had a type 3 and three had a type 4 disease. All patients had at least two autoimmune diseases, and the presence of APA was only a further finding of autoimmunity. APA characteristics, basal and dynamic anterior pituitary function as subsequently specified, and levels of target gland hormones were assessed in each patient at entry and every 12 months until the end of follow-up (5 yr) or the time of onset of pituitary impairment.

All patients developing pituitary dysfunction during follow-up underwent a magnetic resonance imaging of the hypothalamic-pituitary region.

APA assay
As previously described (22), APA were evaluated in patients and in controls by an indirect immunofluorescence method on cryostat sections of young prepubertal baboon pituitary glands supplied by Halifax spa (Polverara, Pordenone, Italy). Fluorescein isothiocyanate conjugated goat antihuman IgG was used to detect the presence of APA, and then positive serum samples were tested with fluorescein isothiocyanate goat antihuman IgG sera.

Anterior pituitary function
At the study entry, basal anterior pituitary hormones (ACTH, FSH, LH, TSH, GH, and PRL) and the respective target organ hormones [cortisol, testosterone, estradiol, free T₄ (FT4), free T₃ (FT3), and IGF-I] were measured in all patients. Dynamic evaluations (1 μg tetracosactide test and GH+arginine test for cortisol and GH, respectively) were also performed.
ACTH deficiency, in the presence of normal or low basal serum levels of ACTH, was suspected when the 0800 h cortisol level was less than 193 nmol/liter and was confirmed by an impaired cortisol response to the 1 μg tetracosactide test (<497 nmol/liter) as previously described (24). GH deficiency (GHD) was diagnosed in the presence of low-normal basal IGF-I and impaired GH response to the GHRH + arginine test. Severe GHD was defined as a GH peak below 9.0 μg/liter, and mild GHD as a GH peak ranging from 10.0 to 16.0 μg/liter (24, 25). Gonadotropin deficiency was diagnosed in males when basal testosterone levels were below the normal range (total testosterone <9 nmol/liter) in the presence of normal or low gonadotropin levels. A similar diagnosis in females was supported by serum estradiol levels lower than 40 pmol/liter associated with inappropriately low serum gonadotropin concentrations. TSH deficiency was established by low serum levels of FT4 (<10 pmol/liter) with serum TSH in the low-normal range. Despite the serum levels of TSH, FT3 and FT4 were measured in all patients; this evaluation might have missed TSH deficiency in those patients receiving treatment for primary hypothyroidism or hyperthyroidism.

Statistical analysis
Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL). Between-group comparisons were performed by Student t test for unpaired data and Mann-Whitney U test according to a normal or a nonparametric distribution of the variable tested. Frequencies among groups were compared by χ2 test with Fisher’s correction, when appropriate. Wilcoxon test was used for within-group comparison. Kaplan-Meier estimates were used to generate overall survival curves for development of pituitary dysfunctions. Differences between groups were assessed by log-rank test. To test the effects of different variables independently of a covariate, Cox regression analysis was used, and partial correlation coefficients were computed. A P value <0.05 was considered statistically significant. Results are expressed as mean ± SD, unless otherwise stated.

Results
At enrollment, in the group of 149 APA-positive patients, 99 (66.4%) sera produced a pattern characterized by the cytoplasmatic immunostaining of a few isolated pituitary cells (type 1 pattern; Fig. 1A). The remaining 50 sera (33.6%) produced a diffuse immunostaining pattern involving all cells in the pituitary section (type 2 pattern; Fig. 1B).

During the follow-up, 28 of 149 (18.8%) APA-positive patients, but none of the 50 APA-negative patients, developed an impairment of the anterior pituitary function. In details, 18 of the 28 patients (64.8%) showed hypopituitarism confined to one pituitary hormone, whereas in the remaining 10 patients (35.2%), pituitary failure involved two or more pituitary hormones. The clinical phenotype of pituitary functional impairment is summarized in Table 2. Briefly, isolated and/or combined GHD was found in 18 patients (64.3%), hypogonadotropic hypogonadism in 11 patients (39.2%), and secondary hypoadrenalism in nine patients (32.1%); however, none of the patients with hypopituitarism showed alterations at magnetic resonance imaging of the hypothalamic-pituitary region. Lifetime analysis was performed after stratification of all patients in relation to the presence or the absence of APA. The curves of cumulative survival for developing pituitary failure demonstrated a significantly different rate (log rank test, P < 0.005) of patients developing hypopituitarism in relation to the presence of positive and negative tests for APA (18.8 vs. 0%, respectively) (Fig. 2A). The 149 APA-positive patients were further stratified in relation to the immunostaining pattern produced by their sera. Lifetime analysis performed for patients showing a type 1 and type 2 pattern of immunostaining revealed significant differences. Indeed, hypopituitarism occurred in 28 of 99 (28.3%) patients with a type 1 pattern and in none of the 50 (0%) patients showing a type 2 pattern, (log rank test, P < 0.0001) (Fig. 2B).

An additional aim of this study was to evaluate the potential clinical significance of different APA titers. As shown in Fig. 2C, in patients with a type 1 pattern, the curves of cumulative survival for developing pituitary fail-
ure demonstrated a significantly higher occurrence of hypopituitarism in relation to increasing titers of APA: 3.7% in patients with an APA titer of 1:8; 21.1% in patients with an APA titer of 1:16; 85.7% in patients with an APA titer of 1:32; 77.8% in patients with an APA titer of 1:64, and 100% in patients with an APA titer of 1:128 (log rank test, $P < 0.000001$).

Cox regression analysis performed by entering the occurrence of hypopituitarism in patients with APA-positive tests and showing a type 1 pattern of immunostaining as dependent variable, and sex, age, basal PRL, cortisol, FSH, LH, FT4, FT3, TSH, the GH response to GHRH/arginine test, the cortisol response to 1 g tetracosactide tests, and the APA titers as covariates clearly demonstrated that the APA titer was the only parameter positively and significantly related to the development of hypopituitarism (Table 3).

As a last step, the basal titers of APA were compared between patients with a type 1 pattern and a type 2 pattern. At study entry, patients with a type 2 pattern showed a significantly higher median APA titer [1:32 (1:8–1:128)], than patients with a type 1 pattern [1:8 (1:8–1:128)], ($P < 0.0005$).

The behavior of APA titers, as measured at the beginning of the study and during the follow-up, was different in patients with type 1 and type 2 patterns. In patients with the type 1 pattern, APA titers also behaved differently in relation to their pituitary functional status. As depicted in Fig. 3, patients with a type 1 pattern who developed hypopituitarism showed a significant ($P < 0.0001$) increase of the median APA titer (Fig. 3A). No significant change in the median titer of APA was observed in patients with a type 1 pattern who did not develop anterior pituitary hormone deficiency (Fig. 3B). In these patients, the behavior of the APA titer was variable, with 17 of 71 patients (23.9%) showing an increase of the titer and most patients

### TABLE 2. Clinical and laboratory features of APA-positive patients developing hypopituitarism

<table>
<thead>
<tr>
<th>Characteristics/findings</th>
<th>Value</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
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<td></td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>21–42</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>31.8 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>10</td>
<td>35.7</td>
</tr>
<tr>
<td>Females</td>
<td>18</td>
<td>64.3</td>
</tr>
<tr>
<td>Hormone deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>18</td>
<td>64.3</td>
</tr>
<tr>
<td>GH$^a$</td>
<td>10</td>
<td>35.7</td>
</tr>
<tr>
<td>LH/FSH$^b$</td>
<td>6</td>
<td>21.4</td>
</tr>
<tr>
<td>ACTH$^c$</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Combined</td>
<td>10</td>
<td>35.7</td>
</tr>
<tr>
<td>GH + ACTH</td>
<td>5</td>
<td>17.8</td>
</tr>
<tr>
<td>GH + LH/FSH</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>LH/FSH + ACTH</td>
<td>2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

$^a$ As diagnosed according to a serum level of GH in response to GHRH + arginine ranging from 8.6 to 7.4 μg/liter.

$^b$ As diagnosed according to serum levels of LH and FSH ranging from 2.1 to 0.7 and 2.1 to 0.4 mIU/ml, respectively, and to testosterone serum levels (in the five male patients) from 6.9–5.2 nmol/liter and estradiol serum levels (in the six female patients) from 36.7–31.8 pmol/liter.

$^c$ As diagnosed according to a serum cortisol level in response to tetracosactide test 1 μg, ranging from 360 to 290 nmol/liter.
showing a decrease (21 of 71 patients, 29.6%) or a stability (33 of 71 patients, 46.5%) of APA titers. By contrast, in patients with a type 2 pattern, a significant \((P < 0.005)\) decrease of the APA titer was observed throughout the follow-up, with eight of 50 (16%) becoming negative for APA (Fig. 3C).

**Discussion**

This longitudinal study, performed on a large cohort of patients with APS and normal pituitary function at entry, was aimed at investigating for the first time the risk of developing hypopituitarism in relation to the presence of APA. By taking into account the different staining pattern at immunofluorescence and the APA titers, a new approach is proposed for assigning a risk score to the development of hypopituitarism in patients with circulating APA. Our results demonstrate that the association of a particular immunostaining pattern (type 1) with the presence of APA at high titer significantly improves the diagnostic value of APA in predicting the occurrence of pituitary autoimmune deficiency.

The identification of patients at high risk for developing clinically overt diseases is an important goal for predicting the clinical course of organ-specific autoimmune diseases (8, 26–28). In this view, whereas the presence of antithyroid and antiaadrenal autoantibodies and their specific titers is considered a good marker for predicting a dysfunction of the respective target gland, the effective value of APA, as measured by immunofluorescence, for predicting
pituitary function impairment is still discussed (16). Previously reported discrepant results are at least in part due to methodological problems. The limited availability of human pituitary specimens, the heterogeneous immunostaining pattern, and the reported presence of positive APA tests in some patients with nonautoimmune pituitary disease clearly reduce the specificity and sensitivity of the APA test. As a result, the predictive value of these antibodies is still questioned (29, 30). In the current study and in previous studies, pituitary sections from prepubertal young baboons, which are thought to be a suitable substitute for human pituitary, were used to search for APA in sera by the immunofluorescence method (31, 32).

The first result of our study for developing hypopituitarism was that APA-negative as opposed to APA-positive patients are not at risk throughout a 5-yr follow-up. In agreement with previous studies (22), we found that the positivity for APA in APS patients is characterized by two distinct patterns of immunofluorescence. The crucial message of this longitudinal study emerges from the relationship between the basal immunostaining pattern and the onset of hypopituitarism during the follow-up of patients with positive APA tests. Indeed, in all of the 28 patients who developed hypopituitarism during the follow-up, a type 1 pattern of immunostaining was observed. On the contrary, none of the patients with serum APA producing a type 2 pattern developed hypopituitarism throughout the follow-up.

The design of the current study does not allow drawing firm conclusions on why the presence of APA at similar titer would be associated with a higher or a lower risk for developing hypopituitarism in relation to the specific pattern observed at immunofluorescence. However, our results would suggest that a diffuse immunofluorescence pattern, being not predictive for future pituitary dysfunction, should be regarded as a nonspecific finding. This hypothesis seems supported by the finding that a significant decrease (with a disappearance in nearly 20% of patients) of the APA titers was exclusively observed in patients with a type 2 pattern. Addressing this issue will remain difficult until the true pituitary antigens responsible for the autoimmune response will be clarified. The recent identification of putative pituitary antigens (33, 34), as well as the future identification of other pituitary antigens, will permit clarifying whether a type 1 and a type 2 immunostaining pattern is sustained by antibodies directed toward specific pituitary antigens or toward non-specific antigens, respectively.

The clinical significance of the APA titer in patients with a type 1 immunostaining pattern is a further point to be discussed. In our previous studies on APA detection, an arbitrary cutoff for positivity of 1:8 was fixed to discriminate the true from the possible false-positive results. We also proposed that APA should be considered effective diagnostic markers of autoimmune pituitary dysfunction only when detected at high titer (35).

In the present study, the results of the Kaplan-Meier curves clearly indicated that the APA titer has little clinical utility if the immunostaining pattern is not taken into account. Indeed, a significantly higher rate and an earlier occurrence of hypopituitarism in relation with increasing titers of APA was observed only when APA positivity was sustained by a type 1 pattern.

Cox regression clearly indicated that in patients with positive tests for APA and a type 1 pattern, the risk for developing hypopituitarism significantly increases in relation with increasing titers of APA. The multiple regression model used allows concluding that higher APA titers are significantly related to the occurrence of hypopituitarism not only in terms of percentages of patients developing anterior pituitary dysfunction but also in terms of the time of occurrence. Indeed, among patients with a type 1 pattern of immunostaining, those with higher titers of APA developed hypopituitarism more frequently and more rapidly than those with lower degrees of positivity for APA.

Patients with positive tests for APA and a type 2 pattern did not develop hypopituitarism throughout the study span independently from the APA titer.

From a clinical point of view, we would like to point out that the lack of detection of secondary hypothyroidism in our series should be taken with caution. Indeed, some patients in our series had a primary autoimmune thyroid disease (either hypothyroidism or hyperthyroidism), thus limiting the possibility to detect inappropriate TSH secretion due to interference of the disease and its therapy. However, patients who were euthyroid and untreated at the study entry remained so throughout the study. The finding of the prevalence of GHD in our patients with autoimmune hypothyroidism appropriately corrected with replacement therapy at entry is apparently in contrast with the results of an important recent paper by Eskes et al. (36). These authors found a prevalence of GHD of 0.4% in a large cohort of patients with autoimmune hypothyroidism corrected with l-T4 therapy. The higher prevalence of GHD, isolated or associated with other pituitary alterations in our study, could be explained by taking into account that none of our patients had an isolated autoimmune hypothyroidism because all fell into APS type 3, thus being more prone to other autoimmune diseases, including those involving the pituitary gland.

Another point that remains to be clarified is to identify which pituitary-secreting cells are identified by APA with type 1 pattern and to match them with the development of particular pituitary failure. The lack of the findings by a
four-layer double immunofluorescence method in APA-positive sera with a type 1 immunostaining pattern does not allow us to draw a firm conclusion about this. However, in previous studies in patients positive for APA with idiopathic GHD (35) and in patients with idiopathic hypogonadotropic hypogonadism (32), the four-layer double immunofluorescence technique evidenced that the pituitary cells targeted by these antibodies were GH-secreting and gonadotropin-secreting cells, respectively. In these cases, the immunofluorescence pattern was that described as type 1 pattern in the present paper, thus suggesting a possible causal relationship with the type of hypopituitarism even if the lack of findings by four-layer immunofluorescence technique in the present study suggests caution against generalization of our assumption.

In conclusion, our results would indicate that: 1) the combined assessment of the immunostaining pattern and the titer of APA by indirect immunofluorescence is a reliable method for identifying patients more prone to develop hypopituitarism. 2) Patients with a type 1 pattern, especially when high titers of APA are found, require a more strict pituitary function surveillance to detect a preclinical phase of hypopituitarism and to interrupt therapeutically, if possible, the progression to clinically overt disease. And 3) the prevalence of pituitary autoimmunity in APS type 3 and type 4 could be higher than that considered so far.

Acknowledgments

In addition to the authors, the following members of the Italian Autoimmune Hypophysitis Network Study contributed to the collection of data and blood samples from patients with autoimmune pituitary diseases: M. R. Ambrosio (Ferrara), E. Arvat (Turin), P. Bini V, Beck-Peccoz P, Bizzarro A, Dotta F, Mantero F, Bellastella A, Betterle C, Santeusanio F 2004 SIE Addison Study Group Italian Addison network study: update of diagnostic criteria for the etiological classification of primary adrenal insufficiency. J Clin Endocrinol Metab 89:1598–1604

M. Delvecchio (S Giovanni Rotondo).

In the present paper, thus suggesting a possible causal relationship with the type of hypopituitarism even if the lack of findings by four-layer immunofluorescence technique in the present study suggests caution against generalization of our assumption.

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