

# Is autoimmune pituitary disease underdiagnosed?

**Original article** Manetti L *et al.* (2007) Prevalence and functional significance of antipituitary antibodies in patients with autoimmune and non-autoimmune thyroid diseases. *J Clin Endocrinol Metab* 92: 2176–2181

## SYNOPSIS

**KEYWORDS** anti-pituitary antibody, autoimmune thyroid disease, growth hormone deficiency, hypophysitis

### BACKGROUND

Although frequently isolated, autoimmune thyroid disease (AITD) can also be associated with other autoimmune disorders, such as hypophysitis, which might result in pituitary dysfunction. Nonetheless, the prevalence of pituitary autoimmunity in AITD remains poorly characterized.

### OBJECTIVE

To determine the prevalence and functional consequences of anti-pituitary antibody (APA)-positivity in patients with AITD.

### DESIGN AND INTERVENTION

This was a health survey of unselected patients with thyroid disease who attended a single center in Italy between January 2004 and August 2005. Thyroid function tests and thyroid ultrasound were performed in all patients. AITD was defined as the presence of thyroid autoantibodies and a hypoechoic pattern by ultrasonography. APA titers were determined by indirect immunofluorescence and a titer >1:10 was considered positive. APA-positive patients underwent pituitary function assessment by measurement of basal and stimulated pituitary hormone levels. Selected patients also undertook a water deprivation test. In normal weight individuals, mild growth hormone deficiency (GHD) was defined as a peak response to growth-hormone-releasing hormone plus arginine of <16 µg/l, whereas severe GHD was defined as a peak response <9 µg/l. Appropriate cut-off values were applied for the diagnosis of GHD in overweight and obese individuals. All patients found to have

pituitary function defects underwent MRI of the hypothalamic–pituitary region.

### OUTCOME MEASURES

The main outcome measures were the prevalence of APA-positivity and the effect of APA-positivity on pituitary function.

### RESULTS

The study group comprised 1,290 patients with thyroid disease (1,099 women) and 135 healthy controls. Of the patients with thyroid disease, 961 had AITD (707 with Hashimoto's thyroiditis and 254 with Graves' disease) and 329 had non-AITD (60 with toxic nodular goiter and 269 with nontoxic nodular goiter). The prevalence of APA-positivity was greater in the AITD patient group than in the non-AITD patient group (11.4% versus 0.9%,  $P < 0.0001$ ). None of the healthy control individuals was APA-positive. Patients with Hashimoto's thyroiditis were more likely to be APA-positive than those with Graves' disease (13.0% versus 7.1%,  $P = 0.005$ ). Overall, 81.8% of the APA-positive patients had previously been diagnosed with isolated AITD. Functional pituitary assessment demonstrated that 36 (35.2%) of the APA-positive patients had mild or severe GHD. Patients with high APA titers were more likely to have GHD than patients with low APA titers. One patient was diagnosed with diabetes insipidus; however, no other anterior pituitary defects were detected in the APA-positive subgroup. MRI abnormalities were detected in 66.6% of patients with severe GHD and 50.0% of patients with mild GHD.

### CONCLUSION

A high prevalence of APA-positivity was detected in patients with AITD, particularly those with Hashimoto's thyroiditis. The presence of APA correlated with an increased incidence of GHD, which suggests that patients with AITD should be routinely monitored for pituitary dysfunction.

## COMMENTARY

## Shereen Ezzat

Patients with AITD and persistent symptomatic complaints—despite normalization of thyroid hormone levels—represent a common endocrine problem. The report by Manetti *et al.* suggests that such patients might suffer from an underdiagnosed entity of endocrine autoimmunity that involves the pituitary. If their estimates can be extrapolated, ~10% of all patients with AITD are APA-positive. Although the association between AITD and pituitary disease is widely recognized,<sup>1</sup> what stands out in this report is the relatively large prospective examination of APA detection in patients with confirmed AITD. More importantly, the authors demonstrate that ~35% of APA-positive patients show evidence of some degree of GHD and/or MRI abnormalities as possible indicators of hypophysitis.

Only a few hundred cases of hypophysitis have been reported since its initial description in 1962. Women are traditionally regarded as more frequently affected than men, particularly during late pregnancy or the early postpartum period.<sup>2</sup> Diagnosis of hypophysitis has been challenging because of the limited tools available. The original APA assays are now regarded as nonspecific, and their use is restricted by limited access. Manetti *et al.* used an immunofluorescence-based APA assay, which could have potentially identified the type of anterior pituitary cell affected. Unfortunately, however, we do not know if pituitary hormonal deficits are related to selective pituitary cell attack (i.e. attack on somatotrophs leading to GHD).

*In vitro* transcription and translation assays offer the prospect of more-specific antigen detection, and  $\alpha$ -enolase and tudor domain-containing protein 6 have emerged as novel pituitary autoantigens.<sup>3,4</sup> The ability of these new assays to identify hypophysitis in general, and in patients with AITD in particular, will require validation. Until then other ancillary diagnostic approaches, such as MRI, must be considered. Unfortunately, MRI findings in proven cases of hypophysitis are extremely variable, and range from complete absence of any abnormality to pituitary stalk thickening to a discrete sellar mass.<sup>2</sup> Diagnosis in the setting of autoimmune disease has, therefore, rested mainly on surgical biopsy and histologic examination.

At least three main clinico-pathologic forms of hypophysitis have been described histologically: lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis.<sup>5</sup> Lymphocytic hypophysitis is the most common type, and is characterized by diffuse infiltration of the pituitary by a mixed population of chronic inflammatory cells, with oncocyctic change of parenchymal cells, and variable amounts of fibrosis. Although the exact pathogenesis of lymphocytic hypophysitis is unknown, it is widely suspected to be an autoimmune phenomenon. In a review of 16 histologically confirmed cases,<sup>2</sup> the most common clinical manifestations were hypopituitarism (63%), mass effects (56%), hyperprolactinemia (38%), and diabetes insipidus (19%). Progressive unrecognized and untreated hypopituitarism resulted in death in at least three patients.

The concomitant occurrence of hormone excess and/or deficiency accompanied by a pituitary mass frequently leads to a diagnosis of pituitary adenoma. The presence of marked hyperprolactinemia usually indicates a prolactinoma, which requires long-term medical therapy. Given the current controversy about the cardiovascular safety of dopamine agonists, the diagnostic accuracy of a presumed prolactinoma will become more clinically relevant. Consideration of other diagnoses in patients with hyperprolactinemia or symptomatic AITD might previously have been regarded as an academic exercise. If the report by Manetti *et al.* is confirmed by additional prospective studies, however, autoimmune hypophysitis must emerge as one of the more common diagnoses in clinical endocrinology.

## References

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## Competing interests

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## PRACTICE POINT

Autoimmune involvement of the pituitary gland should be suspected in patients with AITD, particularly those for whom symptomatic relief is not achieved with thyroid hormone replacement alone