

Editorial: Autoimmune Hypophysitis: An Underestimated Disease in Search of Its Autoantigen(s)

Autoimmune diseases encompass about 85 conditions in which the patient's own immune system attacks itself, rather than foreign, antigens and directly causes pathology. These diseases can affect virtually any site in the body and are now among the top 10 causes of morbidity in women (1). Some autoimmune diseases, such as Hashimoto's thyroiditis, rheumatoid arthritis, Graves' disease, and systemic lupus erythematosus are common, with an estimated population prevalence of approximately 0.5% (2). Others such as birdshot retinochoroidopathy, autoimmune hypoparathyroidism, and relapsing polychondritis are true rarities. Autoimmune diseases tend to cluster in certain families and even occur together, so the presence of one disorder increases the patient's risk of developing a second or a third disorder (3). The common denominator in autoimmune diseases is the mononuclear (mainly lymphocytic) infiltration of the target organ, ultimately leading to destruction of the normal architecture and loss of function. Also common is the presence of circulating autoantibodies, which are much more numerous than autoimmune diseases and are constantly being discovered.

Autoantibodies are at present the only immunological assessment performed in the clinical laboratory to diagnose and monitor autoimmune diseases, because assays aimed at T lymphocytes, often the key pathogenic players, have yet to become mainstream. More recently, autoantibodies have been used to identify individuals at risk for developing a particular autoimmune disease (4). This concept of predictive autoantibodies, now well established for type 1 diabetes, is finding application in an increasing number of autoimmune diseases, opening new opportunities and challenges.

Autoantibodies can be measured by a variety of technologies, including immunofluorescence, immunoblotting, ELISA, fluid phase radioassays, and, more recently, antigen arrays. Immunofluorescence, one of the oldest technologies, is not very sensitive and is based on a subjective and weakly quantitative interpretation of the results. It is useful, however, when the autoantigen(s) recognized by the autoantibodies are not yet known. Immunofluorescence reveals the presence in the patient serum of "histological autoantibodies" that bind to a normal organ or tissue used as substrate. For example, in the mid 1970s autoantibodies reacting against normal human pancreatic islets were found in the serum of patients with type 1 diabetes (5, 6). Subsequently, it was discovered that key autoantigens were the 65-kDa form of glutamic acid decarboxylase and the protein tyrosine phosphatase ICA512. Identification of such autoantigens and "biochemical autoantibodies" has made it possible to de-

velop assays that are objective, sensitive, quantitative, and with high throughput.

This issue of the journal includes a study from the University of Pisa, one of the largest endocrine clinics in Europe, on the prevalence and functional significance of pituitary autoantibodies in patients with autoimmune thyroid diseases. Manetti *et al.* (7) recruited a large number of cases with autoimmune thyroiditis (707 with Hashimoto's thyroiditis and 254 with Graves' disease) and an adequate number of controls (269 nontoxic nodular goiters, 60 toxic nodular goiters, and 135 healthy subjects), and measured cross-sectionally the presence and titer of pituitary autoantibodies by immunofluorescence. They found that pituitary autoantibodies are 12 times more common in thyroiditis patients than in controls (11% *vs.* 0.9% prevalence).

The Pisa study confirms with greater power the findings of six other similar studies (8–13). A meta-analysis of these seven studies shows that pituitary antibodies are, on average, present in about 20% of autoimmune thyroiditis patients. The Mantel-Haenszel pooled estimate indicates that the risk of having pituitary antibodies in patients with autoimmune thyroiditis is 5-fold higher than in controls (95% confidence interval between 3.4- and 7.2-fold). Some study heterogeneity is observed ($P = 0.084$), with one study indicating a 35-fold risk (10) and another a 2.8-fold risk (13), likely due to the use of different methodologies. This heterogeneity is higher when only the Hashimoto's thyroiditis cases are analyzed ($P = 0.002$) and lower when only the Graves' cases are included ($P = 0.400$), perhaps reflecting the fact that the diagnostic criteria of Graves' disease are more uniform than those of Hashimoto's thyroiditis.

The Pisa study also highlights the increasing complexity of pituitary autoimmunity. In their patients, only GH secretion was impaired, whereas the other anterior pituitary hormones (ACTH, TSH, gonadotropins, and prolactin) were unaffected. In contrast, in the classic form of pituitary autoimmunity, called autoimmune (or lymphocytic) hypophysitis, there are typically multiple pituitary defects. Three hundred seventy-nine patients with primary autoimmune hypophysitis have been reported from the original description in 1962 to October 2004 (reviewed in Ref. 14), and 81 additional patients have been identified since then (15). In the total 460 patients, ACTH deficiency is the most common abnormality (present in 57% of the cases), followed by TSH (49%), gonadotropins (52%), GH (39%), and prolactin deficiencies (23%). Patients with histologically proven hypophysitis rarely have isolated deficiencies, such as lacking only ACTH (16, 17) or only TSH (18, 19). In recent years, however, the presence of pituitary antibodies in patients with idiopathic GH deficiency (8) and secondary hypogonadism (20) has been reported, suggesting that the spectrum of autoimmune hypophysitis is wider than previously appreciated. The Pisa

study similarly reports that one third of thyroiditis cases with pituitary autoantibodies also have defective GH secretion and decreased IGF-I, often associated with pituitary abnormalities on magnetic resonance imaging.

It is difficult at this stage to determine whether pituitary antibodies are pathogenic. Traditionally, T lymphocytes are considered the main inducers of damage in organ-specific autoimmune diseases like the autoimmune endocrinopathies. Autoantibodies instead are viewed more as a marker of disease than as its causative agent. Considering that many autoantigens are located within the cytosol, sequestered from blood or lymphatic vessels, it is hard to envision how autoantibodies can penetrate the plasma membrane and make contact with intracellular antigens in sufficient quantities to alter their function. Yet, some autoantibodies do have a well-established pathogenic effect: they can stimulate (as in Graves' disease) or block (as in myasthenia gravis) a plasma membrane receptor; they can bind to a plasma membrane antigen, activate complement, and induce cell lysis (as in hemolytic anemias); or they can couple to soluble antigens and produce damaging immune complexes (as in lupus).

It is even more difficult to determine the mechanisms that lead to the formation of pituitary autoantibodies, or autoantibodies in general. More often, in fact, we understand how immunopathology unfolds but not what causes it. Historically autoimmune diseases have been associated with preceding infections. Notable in this regard is the observation that reovirus type 1 infection in mice induces autoantibodies directed against somatotroph cells that are capable of causing growth retardation (21).

Autoimmune hypophysitis and, more broadly, pituitary autoimmunity remains rare but it is increasingly being recognized. Despite its rarity, autoimmune hypophysitis poses a significant problem because it clinically and radiologically mimics other nonsecreting pituitary masses, such as the much more common pituitary adenomas, which have a population prevalence around 0.1% (22). A presurgical distinction between hypophysitis and the other, nonimmune, pituitary masses would benefit affected patients because hypophysitis can often be managed medically, whereas the other pituitary masses usually require surgical resection. Currently, approximately one half of the hypophysitis patients are misdiagnosed as adenoma (23) and undergo unnecessary transsphenoidal surgery.

Two important challenges need to be overcome to advance our understanding of pituitary autoimmunity. First, we need to identify the pathogenic pituitary autoantigen(s). A pathogenic autoantigen causes disease when attacked by the patient's own immune system, either during the initiation or the effector phase. A pathogenic autoantigen also recreates the human disease when injected into experimental animals in an immunogenic context, *i.e.* along with a powerful adjuvant. This autoantigen in autoimmune hypophysitis awaits identification. Several candidates have been proposed but none has been confirmed in adequate case-control studies, and none has been shown capable of mimicking the human disease in animal models. Candidate autoantigens have been GH, enolase, pituitary gland-specific factors 1 and 2, type 2 deiodinase, and secretogranin (24). Identification of the real pituitary autoantigen(s) may clarify whether pituitary auto-

antibodies are related to the etiology or rather a harmless consequence of the disease. In either case, it will allow the development of a diagnostic serologic test based on the immune pathogenesis of the disease that can be used before surgery in the differential diagnosis of pituitary masses.

Second, we need to establish central disease registries for patients with autoimmune hypophysitis. Without some means of pooling cases, it is difficult for researchers to assemble study populations of sufficient size to conduct statistically meaningful research and develop novel diagnostic tests. A registry would thus serve as a source of well-characterized cases for both basic and clinical scientists, fostering innovation in the field.

In summary, pituitary autoimmunity is likely much more common than previously thought and often associated with important functional defects. We often cite the philosopher Giambattista Vico (1668–1774) by saying "History repeats itself." In the early 1950s my mentor Noel Rose induced lymphocytic infiltration of the thyroid gland by injecting thyroglobulin into rabbits. The pathologist in the group, Kornel Terplan, noted that the lesions were reminiscent of those seen in the "rare" human disease called Hashimoto's thyroiditis. To confirm their findings in humans, the researchers asked endocrinologists in the Buffalo area for sera from Hashimoto's patients. The endocrinologists' reply was "Hashimoto's thyroiditis? We rarely see this kind of patient." And, in fact, it took the researchers about 2 yr to collect just 12 sera (25). Half a century later, our recognition and understanding of Hashimoto's thyroiditis has expanded so much that it has now become the most common autoimmune disease. (It took Manetti *et al.* only 1.5 yr to collect 707 thyroiditis cases!) Who knows, perhaps autoimmune hypophysitis will follow a similar path.

Patrizio Caturegli
Johns Hopkins Pathology
Baltimore, Maryland 21205

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Address all correspondence and requests for reprints to: Patrizio Caturegli, Johns Hopkins Pathology, Ross Building, Room 632, 720 Rutland Avenue, Baltimore, Maryland 21205. E-mail: pcat@jhmi.edu.

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