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Is idiopathic hypoparathyroidism an autoimmune disease?

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Editorial

In 1976, R.M. Blizzard published an article, entitled "Idiopathic Hypoparathyroidism: A Probable Autoimmune Disease" (1). He cited several pieces of evidence supporting his view that this disease is attributable to an autoimmune process. By indirect immunofluorescence, 38% of 74 patients with idiopathic hypoparathyroidism had antibodies to parathyroid tissue. In normal controls, the comparable figure was only 6%. Equally intriguing was the association of hypoparathyroidism with other diseases reputed to be autoimmune in origin. For example, 18 of 32 patients had idiopathic Addison's disease, 7 had pernicious anemia, 2 had premature menopause, 4 had alopecia, and 6 were hypothyroid. In addition, 21 patients had stubborn *Candida* infection.

Recently, Constantin Bona and I decided that, with the newer knowledge gained from cellular and molecular biology, it was time to re-examine the defining criteria for an autoimmune disease (2). Briefly, we proposed that three increasingly stringent levels of evidence were needed to assume that a disease is caused by a pathogenic autoimmune response. The initial level comprises circumstantial evidence, such as the presence of autoantibodies or associations with other autoimmune diseases. The next level includes indirect evidence, such as a parallel induced or spontaneous autoimmune disease reproduced in an experimental animal. These animal models may permit identification of the disease-inducing antigen and allow passive transfer of disease. Species differences in immune responses, however, necessarily limit the use of such animal models in assigning an autoimmune etiology of a human disease.

The most convincing evidence for the autoimmune etiology of a human disease is drawn from instances where the disease can be transferred from person to person. At present, this type of direct proof is only possible for diseases caused by autoantibodies. The necessary steps were well described by Drachman (3) and require that passive transfer of the antibody reproduces the disease features. A few diseases are transferred neonatally from an afflicted mother to her offspring, such as myasthenia gravis. Generally, however, person-to-person transfer is not yet demonstrated. Injections of immunoglobulin from patients with *pemphigus* produce typical skin lesions in new-born mice. Alternatively, antibody from patients can sometimes produce typical, functional changes in vitro, as seen in Graves' disease. Thus the pathogenic effect of anti-receptor antibodies can be determined.

Where does hypoparathyroidism fit on this scale of criteria? There has long been circumstantial evidence of its autoimmune etiology. The association with other autoimmune diseases is well established. Multiple endocrine disorders were well described by Maclaren and Blizzard (4). They defined Type I autoimmune polyglandular syndrome by the occurrence of at least two of the three following diseases: hypoparathyroidism, Addison's disease of the adrenal and chronic mucocutaneous candidiasis. The syndrome is frequently accompanied by additional autoimmune disorders in later years, including pernicious anemia, thyroiditis, hypogonadism, chronic active hepatitis, and alopecia. The presence of autoantibodies to parathyroid cells provides further circumstantial evidence of an autoimmune etiology.

In this issue of *The Journal*, Li and colleagues present additional evidence for the association of hypoparathyroidism and autoimmunity (5). They found that sera from many patients with acquired hypoparathyroidism reacted with a 120–140 kD-antigen in human parathyroid gland extracts, which corresponds in size to the calcium-sensing receptor (Ca-SR). They then tested the possibility that Ca-SR itself was the autoantigen, using three different approaches: (*a*) immunoblotting of a membrane fraction of HEK-293 cells transfected with Ca-SR cDNA; (*b*) Ca-SR cDNA translated in vitro; and (*c*) absorption of the reactivity with cell membranes containing Ca-SR. These experiments clearly identified Ca-SR as an autoantigen in acquired hypoparathyroidism.

Although these findings certainly strengthen the suspicion of a role of autoimmunity (in this case, an anti-receptor antibody) in producing the disease, there are some troubling points. Only $\sim$ 56% of the patients have the Ca-SR antibody. The authors correctly argue that the antibody may decline and disappear in the course of the disease, as it does in another autoimmune endocrinopathy, insulin-dependent diabetes mellitus (IDDM). However, IDDM is believed to be mediated by T cells, with the antibodies serving as indicators of the autoimmune response. In the case of hypoparathyroidism, the conjecture is that the disease is due to the anti-receptor antibody. Better analogies are Graves' disease and myasthenia gravis; in anti-receptor diseases, the presence of the antibody seems to be closely related to symptoms.

Next, the authors tested the most positive sera for their effect on live, transfected HEK-293 cells. They were unable to demonstrate an effect as measured by a change in intracellular Ca^{2+} levels. The function of the anti-receptor antibodies in vivo is still uncertain.

These findings leave open the possibility that the anti-receptor antibodies are the consequence but not the initial cause of an autoimmune process. Yet, they may well add to the final picture of autoimmune disease in some patients. A recent publication has identified the thyroid Na^+/I^- cotransporter, an intrinsic thyrocyte membrane protein, as an autoantigen in autoimmune thyroid disease (6). However, we still do not know whether the receptor is able to induce disease.

The final answer to the question posed in our title awaits further investigation to hunt out the initiating autoantigen in hypoparathyroidism.

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