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Review

Autoimmune thyroiditis: Centennial jubilee of a social disease and its comorbidity

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Abstract

The history of autoimmune thyroiditis (AIT) and its role in pathophysiology of transition from adolescent hypothalamic syndrome (obesity with rose striae) into early metabolic syndrome is reviewed. Marfanoid phenotype and chronic disequilibrium between local, autacoid-mediated and systemic, hormone-mediated regulation, typical for inherited connective tissue disorders, may promote this transition. Pathogenetic roles of hyperprolactinemia and cytokine misbalance are evaluated and discussed in its pathogenesis.

Keywords: Adolescents; Autoimmune thyroiditis; Cytokines; Leptin; Marfanoid phenotype; Metabolic syndrome; Obesity; Prolactin; Transforming growth factor

Contents

1. Introduction

It has been repeatedly noticed in medicine that a disease initially considered being rare or endemic appears to be universally spread and socially important. One of examples is HIV infection, which was proposed to call "4 H's syndrome" in 1983, when its nature was still unknown (its first victims registered were Haitians, homosexuals, hemophiliacs and heroin addicts only) [1].

Autoimmune thyroiditis can be regarded as the unique non-infectious example of this kind, once described as a rare endemic thyroid ailment precisely 100 years ago, and nowadays appeared to be, probably, most universally spread human auto-allergic disease.

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2. Hashimoto's discovery: background

In 1904 J. Donath and K. Landsteiner described the first proven antibody-mediated auto-allergic human disorder. It was paroxysmal cold hemolytic anemia in a syphilitic patient [2]. That time the concepts of humoral and cellular immunity were only just born, a role of plasma cells, recently found by P.G. Unna [3], as a source of antibodies was not known, the existence of T-lymphocytes was not known. At the same time, an outstanding Russian pathophysiologist, one of discoverers of natural autoantibodies – E.S. London (1904) already suggested the unitary theory of humoral and cellular immunity, postulating that both have the same source [4].

Thyroidology of that period already had like 75 years of development passed as an area of clinical medicine, but absolutely irrelevant to immunology. Diffuse toxic goiter was known [5] and related to nervous disorders, although more than half a century still had to pass before the future discovery of thyroid-stimulating antibodies [6]. Thanks to research of newly (1909) Nobel-Price winner Th. Kocher, the concept of iodine-deficient etiology of endemic goiter, earlier suggested by G.A. Chatin, has got a broad recognition [7,8]. But the pathologists knew colloid goiter only, resulted from thyroid hyperplasia in lack of iodine. Yet, goiter was common in some areas, where iodine deficit could not exist at all: for example, on Kyushu Island of Japan, famous for the birthplaces of iodine-containing mineral deposits and for attraction of its inhabitants to sea food.

3. Hakaru Hashimoto: one article immortalized

A young surgeon, Hakaru Hashimoto (1881–1934), medical doctor in 3rd generation, the first graduate from recently established Kyushu Imperial University at Fukuoka, clinical resident of the first Japanese neurosurgeon Hayari Miyake (1867–1945) – during 1907–1910 took part in histopathological studies of partially removed thyroid glands (Fig. 1).

In four middle aged women (two had hypothyroidism) he found in thyroid glands unknown pathomorphological signs [9]. H. Hashimoto noticed that in difference with common colloid goiter, these thyroid specimens contained local infiltrates with lymphoid cells. Formation of lymphoid follicles started from germinal centers. The author depicted the changes of thyrocytes with marked diffuse fibrosis around the lymphoid follicles, giant eosinophilic cells and even lymphatic vessels, newly structured within thyroid gland. This histology did not fit with the diagnoses of Graves' disease, von Mikulicz disease, Riedel's chronic thyroiditis, infectious thyroid involvement. Normally lymphocytes are absent in thyroid parenchyma [10]. Earlier such findings had never mentioned. Hashimoto prophetically concluded that there must be an exogenous factor, provoking accumulation of lymphocytes in thyroid. He was sure that a new disease was discovered. He called it "*lymphomatous goiter*" (lat.: struma lymphomatosa) and published his observations (1912) in a

Fig. 1. Hakaru Hashimoto in 1912. Courtesy of Dr. Hiroshi Sato, Kyushu University.

German journal [9]. In this paper he discussed in details (indicating profound knowledge of a subject) all data on thyroid, available to that period, and even anticipated the probable kinship of a new nosological entity with Graves' disease and von Mikulicz' disease, because "round-nucleated cells" were known for their ability to infiltrate various glands. It is especially valuable, because many years had to pass before the recognition of autoimmune nature for all these forms of pathology.

Later Hashimoto had to abandon scientific career, left university and accepted to himself all care of family and rural medical practice of his deceased father. The brilliant début article, which immortalized his name, remained his sole academic paper. In 1934 this countryside family practitioner perished from abdominal typhoid fever, caught from a patient [10–13]. It was a fateful recapitulation of a previous tragedy: death of a discoverer of another autoimmune thyroid disorder Dr. Karl Adolph von Basedow (1799–1854), who perished from epidemic typhus infected on autopsy of a patient [14].

We believe that it was specifically Hashimoto who described one hundred and one year ago, in 1912 *the first cell-mediated human autoimmune disease*. Delayed type of hypersensitivity (DTH), in fact, was medically observed as early as in E. Jenner's publications on smallpox vaccination [15]. But, before Hashimoto not a single DTH-mediated autoimmune disease was known. Autoimmune endocrine disorders also were not yet described to 1912, although London already produced anti-sperm autoantibodies, registered their presence in healthy men (1901) and came to the conclusion that in enhancement of autoimmunity they can alter gonads and cause infertility [4]. It means that Hashimoto can be referred to as a *pioneer of immunoendocrinology*: indeed