Konstantinidis Ioannis, MD, Prof. of Otorhinolaryngology Aristotle University Medical School, Thessalo

President of the Greek Society of Salivary Glands

Konstantinidis Jordan, MD,PhD, Otorhinolaryngologist, LectureratAristotle University MedicalScool, T

General Secretary of the Greek Association of Salivary Glands

Dr Gelis Dimitrios, MD, PhD, DDS, Otorhinolaryngologist, Korinthos,Greece

Member of the Greek Society of Salivary Glands

Yperifanos Dimitrios, MD, Otorhinolaryngologist, Athens,Greece

Member of the Greek Society of Salivary Glands

Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy associated with variable degree of lymphocytic infiltration of the affected organs (primarily salivary and lacrimal glands) and broad clinical manifestations [1]. Sjögren's syndrome is a common autoimmune disorder. Several genetic risk factors such as STAT-4, ILT6 and the haplotype HLA-B8/DR3 have been identified. In addition, there are environmental risk factors, possibly chronic viral infections [2].

The current used criteria for diagnosis of primary Sjogren's syndrome is the American-European consensus. Primary Sjogren's syndrome is an autoimmune disorder characterized by T and B cells infiltration of the salivary and lacrimal glands, which is followed by destruction of the salivary and lachrymal glands and systemic production of autoantibodies to the ribonucleoprotein particles SS-A/Ro and SS-B/La.

The infiltrating cells (T- and B-cells, dendritic cells) interfere with glandular function at several points: destruction of glandular elements by cell-mediated mechanisms; secretion of cytokines that activate pathways bearing the signature of type 1 and 2 interferons; production of autoantibodies that interfere with muscarinic receptors; and secretion of metalloproteinases (MMPs) that interfere with the interaction of the glandular cell with its extracellular matrix, which is necessary for efficient glandular function. As the process progresses, the mucosal surfaces become sites of chronic inflammation and the start of a vicious circle [3].

In the pathophysiology of Sjögren's syndrome T and B cells infiltrate the salivary and lacrimal glands. As a consequence of the destruction of glandular cells by cytotoxic T cells, production of cytokines and autoantibodies inhibiting glandular function, the production of saliva and tears is

decreased. The feeling of dry eyes and mouth is frequently not noticed by the patients.

Therefore, Sjögren's syndrome should also be considered when extraglandular manifestations such as vasculitis, polyneuropathy or arthritis occur, even when the patients do not complain of dry eyes and mouth. Establishing the diagnosis of Sjögren's syndrome requires verification of reduced glandular function, for example using Schirmer's test and the Saxon test.

The confirmation of Sjögren's syndrome as a cause of sicca syndrome is subsequently performed by the detection of autoantibodies against Ro (SS-A) and La (SS-B) and/or by a salivary gland biopsy [2].

Animal models demonstrated the complex interactions between immunologic and nonimmunologic mechanisms in Sjögren's syndrome. Activation of the innate immune system can lead to exocrine dysfunction before or without significant inflammation, whereas in other models, salivary gland function is preserved despite intense inflammatory infiltrates.

Primary or inflammation-related abnormalities in water channels contribute to the exocrinopathy. Activation of the innate immunity in patients is demonstrated by the upregulation of type-1 interferon-regulated genes (interferon signature) in peripheral blood and salivary glands and abnormal expression of B cell-activating factor and its receptors.

Nonimmune mechanisms that may contribute to exocrine dysfunction include local and systemic androgen deficiency and autonomic nervous system dysfunction. Autoantibodies against the muscarinic acetylcholine receptors would provide a link between autoimmunity and exocrine

dysfunction, but the data on the presence, frequency and physiologic affect of these antibodies remain controversial.

Vitamin D research is discussed in light of the hypothesis that the lower average levels of vitamin D frequently observed in autoimmune disease are not a sign of deficiency. Instead, it is proposed that the lower levels result from chronic infection with intracellular bacteria that dysregulate vitamin D metabolism by causing vitamin D receptor (VDR) dysfunction within phagocytes.

The VDR dysfunction causes a decline in innate immune function that causes susceptibility to additional infections that contribute to disease progression. Evidence has been accumulating that indicates that a number of autoimmune diseases can be reversed by gradually restoring VDR function with the VDR agonist olmesartan and subinhibitory dosages of certain bacteriostatic antibiotics.

Diseases showing favorable responses to treatment so far include systemic lupus erythematosus, rheumatoid arthritis, scleroderma, sarcoidosis, Sjogren's syndrome, autoimmune thyroid disease, psoriasis, ankylosing spondylitis, Reiter's syndrome, type I and II diabetes mellitus, and uveitis.

Disease reversal using this approach requires limitation of vitamin D in order to avoid contributing to dysfunction of nuclear receptors and subsequent negative consequences for immune and endocrine function. Immunopathological reactions accompanying bacterial cell death require a gradual elimination of pathogens over several years [5].

SUMMARY: Recent discoveries from studies in patients with Sjögren's syndrome and animal models suggest a complex interplay between genetic factors, environmental and stochastic events that involve innate and adaptive immunity, hormonal mechanisms and the autonomic

nervous system. Some of these findings suggest that exocrine gland dysfunction may precede autoimmunity or represent a process independent from inflammation in the pathogenesis of Sjögren's syndrome [4].

Despite extensive study of the underlying cause of Sjogren's syndrome, the pathogenesis remains obscure. In broad terms, pathogenesis is multifactorial; environmental factors are thought to trigger inflammation in individuals with a genetic predisposition to the disorder [2].

References

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