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Abstract on the PhD thesis:

The study of Graves' Orbitopathy: clinical evaluation, the role of TSH-receptor antibodies and serum interleukins in the pathogenesis and evolution of disease

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Introduction: Graves' Orbitopathy (GO) represents a special endocrine disorder by its localization, symptoms and evolution. It is an autoimmune inflammatory disease affecting the orbit and soft tissues around the eye, mostly associated with Graves' disease. The ocular manifestations include eyelid retraction, swelling, erythema, exophthalmos associated with conjunctival redness, chemosis, and more rarely altered ocular motility or sight-threatening complications (corneal lesions, optic neuropathy). Clinical evaluation of patients relies on assessing severity and activity by NOSPECS stages and Clinical Activity Score.

The general part of this paper focuses on the current knowledge on the pathogenesis of Graves' Orbitopathy. The main elements are represented by the immune response against an autoantigen (presumably the TSH-receptor), which triggers a cascade of inflammatory changes involving immune cells and a variety of cytokines. These cytokines interact with the orbital fibroblast, leading to its activation, proliferation and differentiation toward adipocytes, resulting in "de novo" adipogenesis. The activated fibroblasts produce glycosaminoglycans, leading to expansion of the orbital tissues and proptosis of the eye(s).

The second part consists of the personal study on patients with Graves' Orbitopathy.

The aim of the study was a.) to present a simple, clinical evaluation methodology of patients, in collaboration with ophthalmologists, b.) to describe the clinical features in relation to age, gender, severity stages and activity score, evaluating the effect of smoking on the studied parameters, c.) to evaluate the role of TSH-receptor antibodies in relation to age, gender, severity and activity and d.) to determine a serologic interleukin profile of these patients with regards on clinical aspects and treatment options.

Material and methods: This was an observational study on 35 patients with Graves' Orbitopathy hospitalized in the Endocrinology Clinical Department during 2007-2010. The selection of patients was made upon the clinical and biochemical markers of autoimmune thyroid disease at onset or under treatment, the presence of ophthalmopathy, ophthalmologic exam and determination of TSH-receptor antibodies. Exclusion criteria were represented by

old Graves' orbitopathy, with previous glucocorticoid treatment and acute disease or known autoimmune disorders. Serum interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-8, interleukin-10, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF- α) and interferon-gamma (IFN- γ) were measured by using a commercially available Biochip Array kit.

Results: 45.71% of patients were male, 54.29% were female, mean age was 44.02 years. Smoking was recorded in 54.29% of cases. 22.9% of patients had mild ophthalmopathy, 51.4% moderate and 25.7% severe disease. 23 patients had active (clinical activity score ≥ 4), 12 inactive GO. Severity defined by NOSPECS stages correlated with Clinical Activity Score ($p=0.025$). Male patients had more advanced disease, when compared to females ($p=0.004$), and there were more male smokers in severe stages (66.6%) compared to female smokers (22.2%). Male patients had a relative risk of 3.65 for developing active disease, and among smokers the relative risk for active GO was 2.42 for male patients. TSH-receptor antibodies (TRAb) proved to be more elevated in active GO ($p=0.024$) compared with inactive cases, and more elevated in male patients compared to female patients ($p=0.041$). There was a positive correlation between median levels of TRAb and Clinical Activity Score ($r^2=0.332$, $p=0.0003$). Female patients had higher IL-8 and IFN- γ , while smoker males higher IL-6 and TNF- α levels. TNF- α levels correlated positively with Clinical Activity Score and TRAb levels. MCP-1 correlated positively with TRAb levels, and IL-1 and IL-4 correlated negatively with TRAb. Regarding IL-6, there was a weak correlation with CAS and TRAb only in male, smoker patients.

Conclusions: Age, male gender and smoking status were associated with more severe and active disease. Smoking represented a risk for active disease in male smokers. TRAb levels correlated with disease activity. Elevated TNF- α and IL-6 levels were found in male patients with more active disease. Women had higher IFN- γ levels, presuming a role of estrogens in autoimmunity.

An extensive and correct evaluation of clinical signs and immunologic parameters is necessary to realize the most appropriate management plan for patients with Graves' orbitopathy.

Keywords: Graves' orbitopathy, clinical activity score, smoking, TSH-receptor antibodies, interleukins.