

Dysthyroid Ophthalmopathy and Related Immunological Disorders

Essay

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Abstract

The immune system does not normally recognize and respond to self antigens, this is due to its ability to differentiate self from non-self antigens, known as self-tolerance. Autoimmunity occurs when there is a failure in the normal mechanism of self-tolerance. This autoimmune reaction is dependent on the presence of cytokines eg. TNF- α and the presence of adhesion molecules eg. VCAM-1.

TED is an autoimmune condition, where T cells and antibodies attack orbital preadipocytes and muscle cells that bear the TSHR protein. It affects the orbital contents including the extraocular muscles and orbital fat. It's the hallmark of Graves' disease. It's characterized by intense inflammation, which includes proliferation and differentiation of fibroblasts to adipocytes, fat deposition and disordered accumulation of GAGs.

Key Words:

Overview on the immune system, Thyroid gland diseases and underlying pathology, Pathophysiology of Thyroid eye disease.

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List of abbreviations:

15-HETE: 15-hydroxyeicosatetraenoic acid

AITD: Autoimmune thyroid disease

AMA: Antimicrosomal antibody test, Antithyroid microsomal antibody test

Anti-NIS: Anti sodium iodide symporter

Anti-TPO: Anti thyroid peroxidase antibody

APCs: Antigen presenting cells

BCVA: Best corrected visual acuity

COX-2: Cyclooxygenase 2

CSF: Cerebrospinal fluid

CT: Computed tomography

CTLA-4: Cytotoxic T- lymphocyte antigen-4

EC: Endothelial cells

FTI: Free thyroxine index

GAGs: Glycosaminoglycans

GO: Graves' ophthalmopathy

HLA: Human leucocytic antigen

ICAM-1: Intercellular adhesion molecule-1

ICMA: Immunochemiluminometric assay

IDDM: Insulin dependent diabetes mellitus

IFN- γ : Interferon- γ

IGF-1: Insulin-like growth factor 1

IgG: Immunoglobulin G

IGSF: Immunoglobulin supergene family

IL-12: Interleukin-12

IL-13: Interleukin-13

IL-2: Interleukin- 2

IL-4, -5, -6,-10: Interleukin-4,-5,-6,-10

IMA: Immunometric assay

IOP: Intraocular pressure

IVIg: Intravenous immunoglobulin

LATS: Long acting thyroid stimulator

LATS-p: Long acting thyroid stimulator -protector

LFA-1: Lymphocyte function antigen

MALT: Mucosa associated lymphoid tissue

MG: Myasthenia gravis

MHC: Major histocompatibility complex

MRI: Magnetic resonance imaging

MS: Multiple sclerosis

NIS: Sodium iodide symporter

PHA: Phytohemagglutinin

PPAR γ : Peroxisome proliferator activated receptors

PPRE: Peroxisome proliferator response element

RA: Rheumatoid arthritis

RAI: Radioactive iodine

RIA: Radioimmunoassay

SLE: Systemic lupus erythematosus

SLK: Superior limbic keratoconjunctivitis

T3: Tri-iodothyronine

T3RU: Triiodothyronine resin uptake

T4: Thyroxine

TALT: Thyroid associated lymphoid tissue

TAO: Thyroid associated ophthalmopathy

TBG: Thyroid binding globulin

TBIA: TSH-binding inhibiting antibody

TBII: TSH-binding inhibiting immunoglobulin

TCR: T-cell receptor

TED: Thyroid eye disease

TG: Thyroglobulin

TgAb: Anti-thyroglobulin antibody

TGF- β : Tissue growth factor β

TGI: Thyroid growth immunoglobulins

Th1: T helper type 1

Th2: T helper type 2

TNF- α : Tumor necrosis factor- α

TPO: Thyroid peroxidase

TPOAb: Anti-thyroid peroxidase antibody

TRAb: Thyroid stimulating hormone receptor antibody

TSAb: Thyroid-stimulating antibody

TSH: Thyroid stimulating hormone

TSHR: Thyroid stimulating hormone receptor

TSHRAb: TSH receptor antibody

TSI: Thyroid-stimulating immunoglobulin

TT3: Total T3

TT4: Total T4

US: Ultrasonography

VCAM-1: Vascular cell adhesion molecule-1

VEP: visual evoked potential

VLA-4: Very late antigen-4

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Introduction

Thyroid-eye disease (TED) *is* known as Graves ophthalmopathy, thyroid - associated ophthalmopathy, dysthyroid ophthalmopathy, thyroid orbitopathy , thyrotoxic exophthalmos and other terms .The different terminology is because TED may be associated with hyperthyroidism, euthyroidism or even hypothyroidism¹.

TED is part of an autoimmune process that can affect the orbital, periorbital tissue, the thyroid gland and rarely the pretibial skin or digits. TED may precede, coincide, or follow the systemic complications of dysthyroidism².

TED is an inflammatory disease of the orbital tissues; it's attributed to an autoimmune process where both cellular & humoral immunity play a role. The effects of inflammation mediated through cytokine release include proliferation of fibroblasts with increased deposition of extracellular matrix mucopolysacharrides, as well as collagen production, adipocyte differentiation and proliferation resulting in salt & water retention within the orbital tissue consequently edema, enlargement of the extraocular muscles, and increased volume of the orbital soft tissues occur with ensuing exophthalmos and in some patients compression of the optic nerve³.

The ocular manifestations of TED include eyelid retraction, proptosis, chemosis, periorbital edema and altered ocular motility with significant functional, cosmetic and social consequences. Although most cases of TED do not result in visual loss, TED can cause vision-threatening exposure keratopathy, troublesome diplopia, and compressive optic neuropathy therefore, all ophthalmologists should be able to recognize TED².

Women are five times more likely to be affected by TED than men, but this largely reflects the increased incidence of Graves' disease in women. Once someone has Graves' disease, his or her sex has little effect on the risk. TED is clinically evident in 25-50% of patients with Graves' disease and 3-5% of the cases develop severe eye disease. Men older than 60 may be at increased risk of more severe disease⁴.

The major clinical risk factor for developing TED is smoking, it increases the risk four times than non-smokers, and it's directly related to the number of cigarettes per day. It also increases the risk for progression of ophthalmopathy after radioiodine therapy⁵.

Edema, inflammation and late fibrosis account for the decreased function of the extraocular muscles despite relative preservation of the fibers themselves. The recruitment of T cells to the orbits of these patients may result from the expression of the target of the aberrant immune response in Graves' disease and the TSH receptor in the orbits of patients with TED. The orbital fibroblasts especially those present within patients with TED may be more sensitive to the effects of cytokines accounting for the frequent and relatively selective involvement of the orbit in Graves'disease⁶.

Treatment varies according to the present problem. Variable lines of treatment are available including steroid treatment, prisms, radiotherapy as well as surgical procedures for different cosmetic and functional problems such as orbital decompression, extraocular muscle or lid surgery⁷.

In a study dealing with immunopathogenesis of the disease, immunosuppressant therapy was evaluated. Treatment with glucocorticoids, non-