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Immunological aspects of Graves' disease

Thesis

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By

Dr. Mohamed Majed Abdel-Munieum-

Dweik.

616.479
M.M

Ain Shams University

Faculty of medicine

Supervised by :

Prof. Dr. Kamal El-Shawarbi.

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A C K N O W L E D G E M E N T

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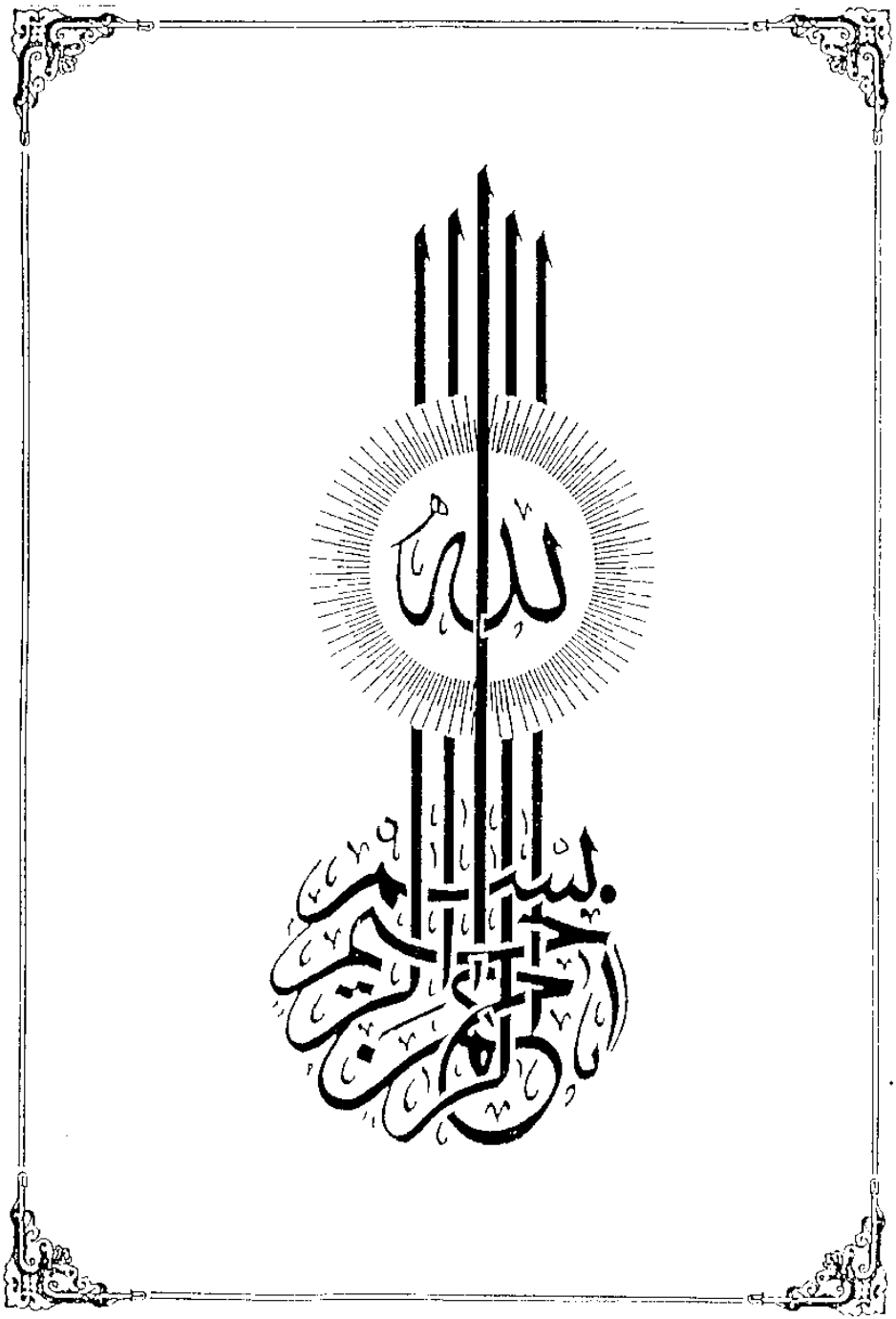

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Immunological Aspects of Graves'Disease

Graves'disease, diffuse toxic goitre, exophthalmic goitre, primary thyrotoxicosis or Basedows' disease is a multisystem disease of unknown atiology, consisting of one or more of three pathognomonic clinical entities : -

1. Hyperthyroidism is a better name than throtoxicosis due to the fact that it is a normal product of the body. This will cause a derangement of the homeostatic mechanisms that normally adjust thyroid hormone secrection to meet the physiologic needs of peripheral tissues by exposing almost all the tissues to hypermetabolic activities.

2. Infiltrative ophthalmopathy and,

3. Infiltrative dermopathy (pretibial myxoedema)

4. It is marked additionally by one of the pathognomonic laboratory findings which is the presence of high titre of long Acting Thyroid Stimulator (LATS).

Aetiological Theories:

1. One of the earliest theories suggested that: because the disease runs in many members of one family: it was considered that there is a genetic factor (Boas and Ober, 1946) which is altered by diseases e.g. by Lobar pneumonia.

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2. Another view postulated that the acute form of thyrotoxicosis was a psychosomatic disease explained on the light of observation that while emotional stress is very common, throtoxicosis is relatively rare[29].

3. Another suggestion was that the homeostatic disruption resulted from either over-production of thyroid stimulating hormone (TSH) by the pituitary or development of autonomous hyperfunction within the thyroid tissue. TSH was invariably undetectable by sensitive radioimmunoassay in the sera of actively thyrotoxic patients, indicating that TSH is not pathogenetically involved[22].

But extremely rare cases of diffuse toxic goitre may be due to hypersecretion of TSH by pituitary adenoma[29].

4. Several features of Grave's disease suggest that the immunological system is involved, e.g lymph nodes enlargement may be present, lymphocytosis is usually found and splenomegaly is detected in about 10% of patients, Thymic enlargement is present in one half of Patients studied at autopsy[29]. These features have been known

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for a long time, but their specific relationship to immunological abnormalities in Grave's disease is still unknown.

"Long Acting Thyroid Stimalator" (L A T S)

A great change in the previous ideas took place in 1956 when Adams and Purves, using a new technique for the assay of TSH, discovered in the sera of the patients with Graves' disease a thyroid stimulator which they called Long Acting Thyroid Stimulator (LATS) that differed from TSH principally in the longer duration of its action in the test animal reaching maximally from 8 to 24 hours, while that of TSH reaches its maximal effect as a thyroid stimulator after 2 hours then declines. It is concluded that the early phase of stimulation of the thyroid by LATS is qualitatively similar to that due to TSH, but has longer latency(38).

There is evidence that LATS is distinguishable from TSH and is not of Pituitary origin, evidenced by the absence of LATS from the pituitary of patients with Grave's disease taken at necropsy and the presence of LATS in the blood of people with hypothyroidism.(31)

In vivo this hormonotropic serum globulin has like TSH many actions, of these:

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- The principal action is the stimulation of hormone relase.
- Increasing the organification and uptake of iodine.
- Inducing thyroid hyperplasia.
- Like TSH it stimulates many aspects of thyroid intermediate metabolism.(38)

Fractionation of serum from thyrotoxic patients soon revealed that LATS resided in globulin fraction and has a sedimentation Coefficient of 7s, More detailed analysis confirmed that it was a true IgG.(46) Both the light and heavy chain are necessary for biologic activity, but the light chain seems to be less specific as it can replaced by a light chain from other IgG molecules. LATS activity is only partially inhibited by antisera to either L or K light chains alone, both antisera combined will produce 100% inhibition of LATS. This suggests that LATS contains both L and K type light chain and therefores not produced by a single clone.(31)

LATS is known to combine with throid tissue. IgG prepared from serum containing LATS inhibits the receptor-binding of $I^{(125)}$ labelled thyrotrophin (TSH) in particulate fraction of guinea-pig thyroid homogenate, LATS, Though able to block recombination of labelled TSH with receptor,

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does not promote dissociation of existing receptor - TSH complexes.(28,30)

The response to TSH in the mouse bioassay is inhibited by the prior administration of LATS (Mc. Kenzie, 1966; Burke, 1968). This suggests that the receptors mediating LATS and TSH actions are closely related.(16)

The all or non effect of LATS on individual receptors suggests that the molar ratio for LATS: Receptor combination is 1 : 1 16.

An important noting is that these actions are away and independent of the pituitary, since they occur even when the recipient animal is hypophysectomised.(46)

In addition LATS, like TSH, induces resorption of colloid and proteolysis of thyroglobulin, and stimulates thyroid glucose oxidation and phospholipids synthesis.(46,29)

There are strong evidences suggesting that these effects (like those of TSH) may be mediated through activatio of adenylcyclase-cyclic AMP system which is membrane bound to thyroid cells.(35) It has been suggested that abnormalities in critical thyroid cellular function e.g. adenylcyclase cAMP binding and or protein Kinase activities may be responsible for the hyper function of the gland in Graves'

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disease. But it is concluded that hyperfunction in Gaves' disease is probably not a result of quantitative or qual-ititative abnormalities in adeny-cyclase-CAMP-protein kinase system.(35)

A series of experiments is reported to test the hypothesis that the LATS of Graves'disease has antibody function, it was not possible to transfer LATS activity to new immunoglobulins G (IgG) molecules. This supports the indea that LATS is an integral part of the IgG molecule. LATS was consistently removed from a thyroid microsomal fraction and eluted from the microsome under conditions appropriate for dissociation of antigen - antibody complexes. The eluted material contained a much larger quantity of LATS proportion to its IgG content than the original sera. These findings were consistent with the hypothesis that LATS is an antibody. However, a mixture of LATS containing sera and thyroid microsome did not fix complement.(11)

Although there exist no doubt that LATS is an antibo its corresponding antigen has not yet been clearly identifie Sera of rabbits immunised against human thyroid microsomes contain a thyroid stimmulating activity similar to that of LATS.(23)

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Attempts to identify the LATS antigen have met with mixed success. A neutralising factor (LATS absorbing activity (LAA) is found in thyroid microsomes and cell sap.(3) Recent evidence suggests that LATS binds to thyroid membrane at sites close to or identical with the TSH receptors.(40,18)

Schieusener (1971), have suggested that the soluble cell-sap component which combines with LATS corresponds to solubilised lipoprotein material from the cell membrane.(46)

LATS now is considered as an auto-antibody directed against some component of the thyroid tissue, many observations indicate that either the soluble or microsomal fraction of thyroid tissue might contain the LATS antigen.(46)

It was suggested by Rotti and Torrigiani, 1967 that thyroglobulin is found in peripheral circulation, in extremely small concentrations which are probably just sufficient to maintain unresponsiveness with tolerance to " T cells "- Thymus dependent lymphocytes - but not to " B cells " - bone marrow dependent lymphocyte. The host would appear compeletely normal since unsesponsiveness at the T cell level is sufficient to keep the host tolerant and inhibit any immune responsewith antibody production.(34)

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Alteration in thyroid tissue may occur by viral or genetic mutation, thus allowing (T cells to react with altered portion of the self antigen, the "T cells" will react with already immunocompetent "B" cells resulting in injury.(34)

Thyroid antigen-antibody system:

The main antigen of the thyroid tissue are : -

1. Thyroglobulin (m.w. 660,000) which is the main storage protein in the colloid of the gland.
2. Microsomal antigen which is found in much higher concentration in thyrotoxic patients. The location of the antigen is the lipoprotein membrane of the apithelial microsome.

It is suggested that LATS reacts with microsomal antigen and not thyroglobulin portion.(34)

Incubation of the serum containing LATS with these fractions leads to an inhibition of the LATS effect.

Circulating lymphocytes from patients with Graves disease were found capale of synthesizing LATS in tissue culture when stimulated with phytohaemoagglutinin (PHA), It is possible that this globulin (produced by lymphocytes)

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acts against the normal inhibitor of mitosis in the thyroid gland, thus removal of mitotic inhibition could lead to hyperplasia, followed by hyperfunction (7, 16, 32).

Circulating lymphocytes do not play an important actiologic role in the pathogenesis of thyroid autoimmune reaction. Lymphocytes inside the thyroid gland may be more important in this process.(16)

Certain collections of data have raised doubt concerning LATS:

1. LATS could be demonstrated in sera of only two thirds of actively thyrotoxic patients with Graves' disease, even when 10 folds IgG concentrates of serum were tested.(22,3,18)

2. The titre of LATS in sera of thyrotoxic patients did not correlate well with the degree of the thyrotoxicosis or with the size of the thyroid gland, but correlated more with the severity of the ophthalmic signs and pretibial myxoedema.(46,3,18) Hetzel and Wall (1969) evaluated the relationship between pretibial myxoedema and LATS level. Whenever the skin lesion is progressing, The LATS level is similarly steady, and when the myxoedema regressed, the plasma LATS level in all cases fell. But the degree of regression

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depends upon the chronicity of the lesion, more chronic lesion with fibrosis and irreversible damage will not show clear cut cure but definite improvement.[24]

3. The pathogenetic factor in diffuse toxic goitre would manifest itself in non suppressibility of thyroid function. However LATS has been demonstrated in the sera of some patients with Graves' disease whose thyroid is normally suppressible, this means that other factors participate.

4. However there is one strong piece of evidence that LATS can cause hyperthyroidism in man. It is almost invariably present in maternal and foetal serum in cases of neonatal thyrotoxicosis and it disappear as the disease remits.[3,18,46]

Recently it was found that sera of some patients with Graves'disease contain IgG that prevents the neutralization of LATS by human thyroid tissue not by mouse thyroid, so there are some protectors suggested (Adams and Kenedy, 1971).[5,2]

After the discovery that LATS can be neutralised by incubation with thyroid glands preparation, it was found that there is a thyroid autoantibody which will compete

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with LATS in neutralization reaction. This LATS - protector doesn't stimulate the mouse thyroid nor interfere with the action of LATS in the mouse. LATS-protector might be a human thyroid stimulating antibody, not cross reactive with mouse thyroid. Human thyroid had always been used to demonstrate the LATS-protector phenomenon. LATS-protector appears to have no reaction with the mouse thyroid either in vivo or in vitro. The finding of LATS-protector so far only in thyrotoxicosis and its presence in 90% of 50 patient with diffuse toxic goitre including all those showing LATS supports the view that it is thyroid stimulator in man and it should be renamed Human Thyroid Stimulating Immunoglobulin (H.T.S.I.). A study of the effect of LATS-protector on the formation of intracellular colloid droplets in human thyroid tissue in vitro has provided the first direct evidence of a stimulating action.(3,18)

Immunogloulin concentrate from normal euthyroid subjects with no history of thyroid disorders failed to show LATS-protector. It is also absent from patients with toxic adenoma. LATS protector was found in all patients, with Graves' disease not showing LATS.(5)

Subsequent work has confirmed that H.T.S.I. is found in the sera of most and possibly all hyperthyroid patients.(10)

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