AIN SHAMS UNIVERSITY
FACULTY OF MEDICINE

Immunoglobulins IgG, IgM, IgE and C_3 & C_4 in serum and ascitic fluid in bilharzial hepatic fibrosis

Thesis

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By

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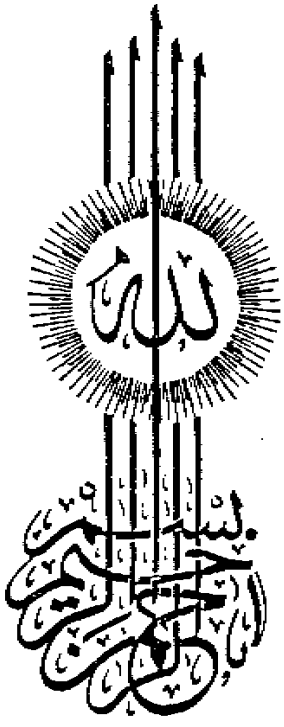

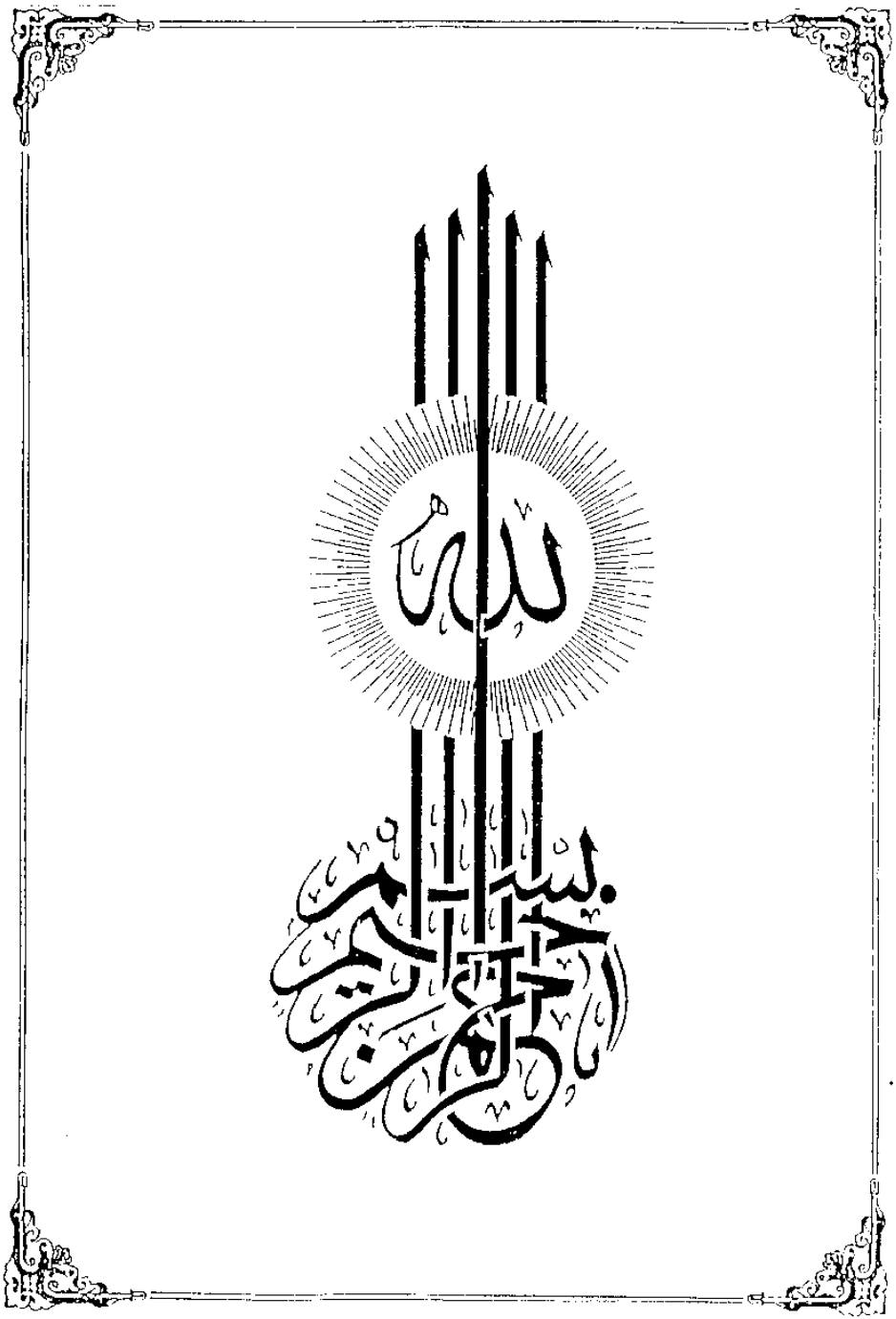

I N D E X

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The Immune System and the Liver:

The liver is of key importance in removing noxious extraneous antigen through its reticuloendothelial network (Kupffer cells). Cells responsible for immune reactivity in liver are:

(1) B lymphocyte, the clone progenitors of plasma cells which secrete immunoglobulins and T lymphocyte which mediate cellular immunity including delayed hypersensitivity.

(2) T. lymphocyte cells help regulate humoral immune response by acting as ptoentiators (helper cell) or inhibitors (suppressor cells) of transition of B cells into immunoglobulin secreting plasma cell. Helper and suppressors cells appear to be distinct subsets of T. cells which can be distinguished by their Ly surfacemembrane antigen. (Jaudinski, et al, Tadakuma, T. et al. 1976). Impaired suppressor T cell function may lead to overt autoimmune disease.

Subsete of low density lipoprotein have been found to possess bioregulatory properties of lymphocyte function.

Rosette inhibitory factor (R I F) and low density lipoprotein inhibitor (L D L In):

Rosette inhibitory factor was first demonstrated in serum from patients with viral hepatitis, it is an inducible minor species of serum low density lipoprotein capable of regulating T cell binding with sheep red cells via the E receptor.

This factor may be responsible for observed reduction of T cells in patients with acute and chronic viral hepatitis. (Chisari, et al, 1975).

Rosette inhibitory factor possesses an unusual apolipoprotein composition and binds with great affinity to limited number of lymphocyte surface receptors that are independent of the sheep erthrocyte receptor.

Low density lipoprotein inhibtor suppresses lymphocyte response to migration and allogenic cells in vitro. (Curtiss, et al, and Edgington, 1977).

Hepatic antigens:

The liver contains organ-specific and organ nonspecific antigens which have been implicated in pathogenesis of liver disease and used in diagnosis:

Nuclear, mitochondria, microsomal, basement-memblane, and bile ductal antibodies have been domenstrated in patients with liver disease. Serologic dectection of these antibodies has been usuful in recognition and follow up of hepatic injury, however they are not specific. (not specific)
Fore Example the antimitachonidrial antibodies which are present in 90% of patients with biliary cirrhosis are useful as screening test, but specific differentiotion of this disease from extra hepatic biliary obsterction requires rediologic visulization of biliary network.

Several organ specific antibodies have been identified in liver disease

* Membrane antigen (lipoprotein I and II), which have been demondstrated in chronic active hepatitis (Meyer Zom Buschenfelde, and Hopf, 1974).

* Cytoplasmic (F) antigen found in viral hepatitis and acute liver cell necrosis. (Rosenmund, 1971)

* Alcoholic hyaline antigen (A H A G) encountered in alcoholic hepatitis. (Chen, T. et al. 1976).

Roles of sensitized lymphocytes in pathogensis of liver disease:

* *Cytotoxicity:*

Lymphocytes are responsible for cytotoxic reaction encountered in liver disease. Both T, B lymphocytes may cause cell lysis. Thus antibody dependent cellular cytotoxicity is due to null cells. (Cochrane, et al, 1974). Activation of cytotoxic lymphocytes (Killer cells) requires the participation of macrophages which function as nonspecific accessory cells. Membrane-membrane bridges exist between sensitized lymphocytes and target cells. Interaction during cytolytic events result in changes in membrane permeability. Within minutes of establishing a contact, membrane of both lymphocytes and target cells exhibit increased permeability to non-protein ions; after longer incubation, there is loss of cytoplasmic protein. (Cerottini, 1977). Resulting intracellular

metabolic dysequilibrium helps foster cell damage or destruction.

* *Fibrogenesis:*

Of equal importance to cytotoxicity in the development of chronic liver disease is collagen deposition and scar formation. Fibroblastic activity, ground substance deposition and collagen synthesis leading to fibrosis is an active process; studies immune mechanisms play a central role in the occurence and perpetuation of hepatic fibrosis, (Chen, et al, 1973). Supernatants of hyperactive lymphocytes added to either cultured fibroblasts or autologous liver causes a significant increase in collagen secretion by microtubules. A fibrogenic lymphokine released by lymphocytes simulated by phytohemagglutinin (PHA), HB_s, Ag, A H A G, or cercarial antigen increases the incorporation of tritiated proline into collagen. Moreover, collagen isolated from alcoholic liver disease and added to lymphocytes from patients with alcoholic hepatitis causes an increase in migration inhibition factor. (Jaudinski, et al 1976). This may explain the progressive fibrosis in patients with chronic liver disease in whom initial etiologic factors are no longer present.

Immune Complexes

Immune complexes are found in liver disease. The domonstration of immune complexes explains the frequent systemic manifistation seen in the liver disease including skin rashes, cutenous hemorrhage, arthralgia, proteinuria, renal failure, thrombocytopenia and hypocomplementemia. (Wands, et al. 1975).

A decrease in complement factor beside C_3, C_6, C_9, C_1 inhibitor which are produced in liver (Colten, 1976) support the pastulate that complement is consumed in the immunologic reactivity independant of liver dysfunction.

The deposition of immune complexes in acute and chronic active hepatitis lead to complement mediated antibody cytotoxicity. Immune complexes may therefore be of key importance to development of hepatic necrosis. Other factor are equally important.

Use of Immunolegic Methods in diagnosis of Liver disease:

(1) Immunologic studies of immunodeficiency and selection and monitoring of treatment.

(2) Tests include those which elaluate:

(A) Humoral immunity (immunoglobulins A, G, M. cryoglobulin, antibodieste to nuclei, mitochondria, microsomes and smooth muscle and Serum complement.

(B) Cell mediated immunity, skin tests, Lymphocyte transformation and production of Lymphokines.

(C) Serologic studies to detect etiolegic factor (hepatitis A and B antigen and antibodies, cercarial antigen and antibodies, and liver speefic antigen.

Type of immunoglobuline:

Immunoglobuline G (Ig G):

This constitute approximately 75 - 80% of immunoglobulins, the normal serum concentration is 0.8 to 1.5 gm/100 cc, molecular weight of these globulins is 150.000 and their CHO content is 2.5%.

The majority of the aquired antibacterial and antiviral antibodies fall in this class, it contains also L.E. factor, cryoglobulin, antibodies of gram+ve. It is resposible for major part of antibodies of second response. It is also protective againist malaria.

The reaction between 1g G and antigen activates a complement system leading to release of several chemical mediators including factors causing immune adherance as well as anaphylactoxins and permeability factors which initiate inflammation and hypersesitivity reaction. studing the serum immunogleblins in schistosomasis mansoni, a statistcally significant rised Ig G (Ain Shams Medical Journal, Cairo, 1974).

Immunoglobulin M (Ig M):

Macroglobulins are so named because of their high molecular weight 900.000, their CHO content is high (10 - 12%) and like Ig A. They tend to polymerize, their normal serum concentration is 0.039 to 0.117 gm%. These globulins include the iso-haemayglutinin, saline RH antibodies, cold haemogglutinin, many of the heterophilic antibodies

and the rheumatiod factors. It has bactericidal activity against gram negative bacteria, high levels of Ig M are found both in blood and cerebrospinal fluid in trypanosomiasis. It forms about 5% of serum immunoglobulin. Statistically rised only in active S. mansoni (Ghamen et al. 1982).

Immunoglobulin E (Ig E):

It is molecular weight is 200.000. It is also a secretory immunoglobulin and is found in serum in trace amounts it fixes to the mast cells and upon reaction with the corresponding antigen lead to injury of the mast cells with release of histamine, serotonin, bradykinin, as well as, slow reaction substance. It has been postulated that Ig E, plays a major role in parasitic immunology.

The basis structure of immunoglobulin molecule is composed of two pairs of polypeptide chains, two light chains with molecular weight of about 20.000 and thus heavy chain with molecular wieght of about 50.000.

All immunodiagnostic tests depends in immunoglobulins Ig E is responsible for the development of the wheal and flare of the immediate skin test.

Ig G share is circumoval precipitin (C. O. P.), gel precipitin, cholesterol - Lecithin flocculation slide flocculation and cercarial hullen reactions. Ig M is active in the indirect haemagglutination and immunoforescent technique. (Freeman et al. 1970).

Immunoglobulin A (Ig A):

Ig A forms only about 15 - 16% of total serum immunoglobulin. It differ from Ig G in their high CHO content (8.5%) and in the fact that they tend to polymerize and form complexes with other serum proteins. Its molecular weight is 150.000 - 170.000, their normal serum level is 0.056 to 0.193 gm%. It is mostly secreted by muscous membranes, and it is the main part of secretory immune system. It contains also some of isohaemagglutinin, antibrucella, and anti-insulin antibodies.

Immunoglobulin D (Ig D):

Molecular weight is 180.000. It contain for 0.4% of total immunoglobulins. Their normal serum concentration is 0.003 gm%. It has unknown fanction.