DECREASED HAPTOGLOBIN LEVEL IN BRONCHIAL ASTHMA

THESIS

Submitted For Partial Fulfillment

Of The Master Degree

In

PEDIATRICS

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1986

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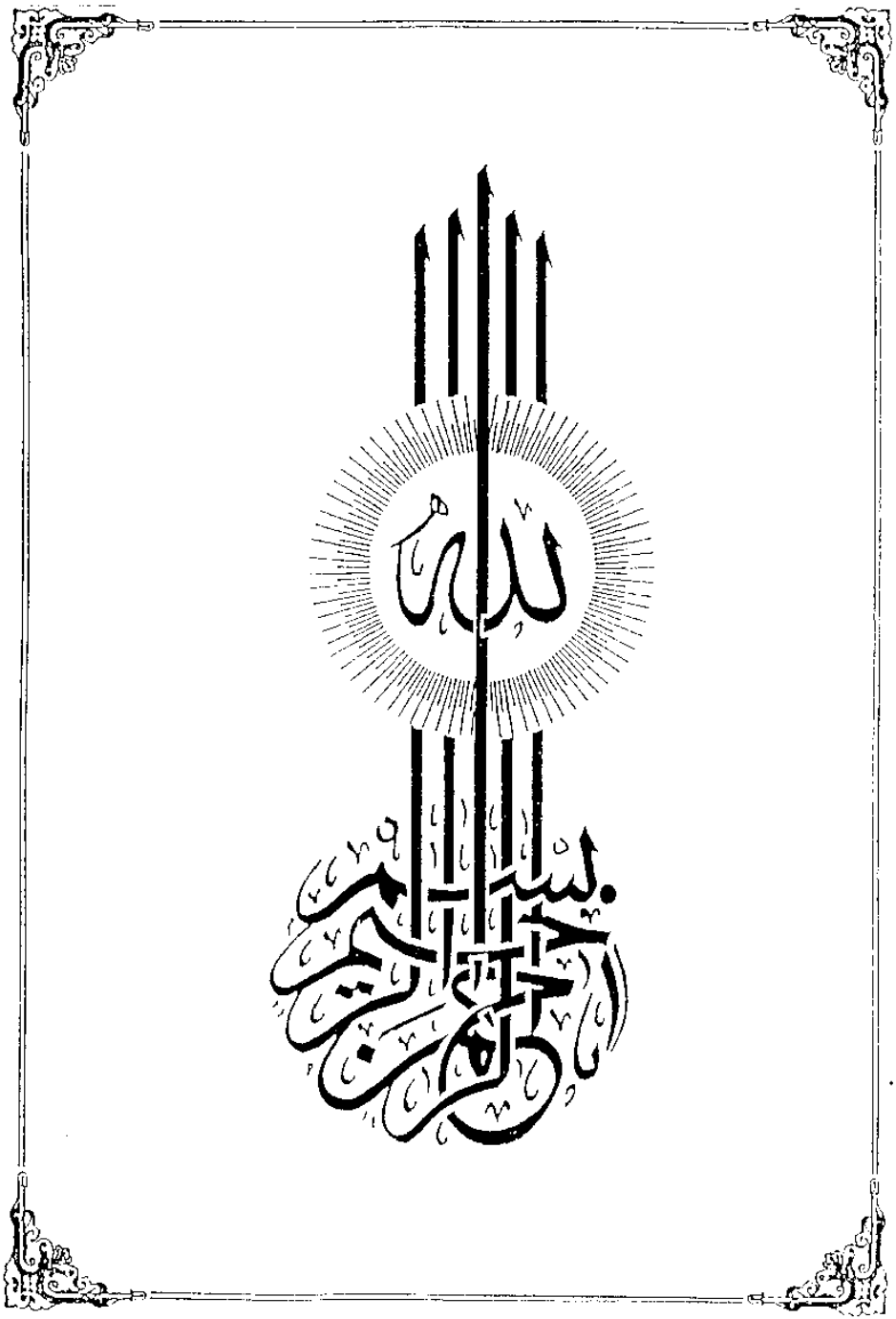

ABBREVIATIONS

EIPS = Endogenous inhibitors of prostaglandin synthetase.

Hb = Haemoglobin

HbBC = Haemoglobin binding capacity

Hp = Haptoglobin

IgE = Immunoglobulin E

PG = Prostaglandins.

S.D. = Standard deviation

X^2 = Chi square

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INTRODUCTION

Haptoglobin [Hp] is a serum globulin, genetically determined by two autosomal codominant allelic genes Hp^1 and Hp^2 [Piessens et al.,1984].

It is a haemoglobin transfer protein, and also a positive acute phase reactant [Toivo,1973].

It has recently been found to inhibit prostaglandin synthetase in animal tissue . Thus low haptoglobin levels may facilitate atopic disease by an increased prostaglandin synthesis . [Saeed et al.,1977,1978,1979 ; Kendal et al., 1979 ; Collier et al.,1980; Denning-Kendal et al.,1980].

Asthma is a clinical disorder characterized by intermittent airway obstruction with symptom free interval. The basic defect is probably bronchial hyperreactivity which can be converted to clinical asthma by a variety of immunological and non immunological stimuli. Immediate hypersensitivity [Type I] involves the release of mediators from reagin -sensitized mast cells, causing increased vascular permeability , oedema and smooth muscle contraction. Prostaglandins are now known to be one of these mediators. So increase of prostaglandins secondary to decreased haptoglobin might be a cause of bronchial asthma.[Simpson et al., 1984].

AIM OF THE WORK

With this idea in mind we aim at determination of the level of Haptoglobin in cases of childhood bronchial asthma to prove its questionable role.

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REVIEW

OF

LITERATURE

HISTORICAL REMARKS

Haptoglobin [Hp] was discovered by polonovski and Jayle in 1938, while studying how the pseudoperoxidase activity of haemoglobin varied with experimental conditions. [Polonovski and Jayle,1938].

They found that serum contained a variable amount of non dializable substance, which under certain conditions made haemoglobin [Hb] behave like a true peroxidase. Since the substance apparantly linked [Hb], they called it haptoglobin [Hp] i.e Haptein = to bind.[Polonovski and Jayle , 1940].

DEFENITION

Haptoglobin is a blood serum protein of the α_2-globulin fractions. Its function is to mediate the recycling of heme iron by forming effectively irreversible but non covalent complex with haemoglobin that has been released from red blood cells into the serum. This complex is rapidly taken by liver cells and digested.[Ignez et al., 1981]. Hp is synthesized by the liver. It is found in several genetic forms, many of which are polymers of the same basic substance. [Bernini and Borri-Voltattorni,1970].

GENETIC CONSIDERATIONS

Haptoglobin is an $_2$- glycoprotein. By starch gel electrophoresis, a number of haptoglobin bands may be observed. The observed pattern reflects the genetic constitution [Smithies, 1955]. Later on it was proposed that there are three haptoglobin phenotypes : 1-1 , 2-1 and 2-2 . It was suggested that a single pair of genes Hp_1 and Hp_2, neither of them is dominant, are responsible for the three genotypes [Hp^1/HP^1] , [Hp^1/Hp^2] and [Hp^2/Hp^2]. [Smithies , 1957].

The pair of genes encoding the Hp is located on chromosome band 16q22. [Mc Gill et al.,1984].

A small percentage of normal adults have no haptoglobin. The frequency of ahaptoglobinemia in normal adults varies from 1% in Denmark and 2% in Britain to 32% in Nigeria. These observations have led to the postulation of a Hp^0 gene responsible for the absence of haptoglobin. [Smithies, 1957].

Giblett and Steinberg[1960] postulated three alleles at the haptoglobin locus : Hp^1, $Hp^2$and Hp^{2M}, the last one is a " modified $Hp^{2"}$ and occuring predominantely, but not exclusively in American blacks. They suggested that the allele

Hp^{2M} in combination with Hp^{1} produces either $Hp^{2-1[m]}$ or ahaptoglobinemia.

Haptoglobin is formed of 2 polypeptide chains and B. The B chain is apparantly the same in all the haptoglobin variants, but the chain is modified as an expression of haptoglobin genes . Later on five different ∝-polypeptides have been identified : hpIF, hpIS, hpZ, hp2j and hp2M. These account for a number of subtypes : Subtypes 1S-1S, 1S-1F and 1F-1F of Hp^{1-1} . Subtypes 2-1S and 2-1S of Hp^{2-1}. It is now thought that these five polypeptides are the expression of five alleles: Hp^{IF}, HP^{IS}, Hp^{2}, Hp^{2J} and Hp^{2M}. Of the 15 possible genotypes, at least 10 phenotypic expressions have been identified .

CHEMICAL STRUCTURE

Haptoglobin is a tetrameric protein, it consists of two different chains repeated once . It has two light [L] or [∝] chains and 2 heavy [H] or [B] chains. [H] and [L] chains differ in size and sequence dramatically and are linked together by disulphide bridges. [Chow et al.,1984]. the genetic variation affects the light chain only ,the heavy chain appears to be identical in all phenotypes. [Conell et al.,1962 ; Clove et al.,1969; Barnett et al.,1970].

In humans, the [L] chains occur in two major allelic forms [L^1] with 83 residues and [L^2] with 142 residues. As a result three human genotypes exist, Hp^{1-1} which is homozygous for [L^1] , Hp^{2-2} which is Homozygous for [L^2] and Hp^{2-1} wjocj os heterozygous [Ignez et al.,1981]. The [H] chain consists of 245 residues and has four carbohydrate chains attached, which comprise 19.4 % of the molecular weight of this chain .

The carbohydrate content of haptoglobin is made of six moles of hexose [glucose or mannose or both],3-4 moles of glucosamine and 0.3 moles of N-acetyl neuraminic acid for one mole of haptoglobin.[Corbeck et al.,1967].

Electron microscopy shows that haptoglobin has the shape of barbell with two spherical head groups, which are the [H] chains . These are connected by athin filament with a central knob, which corresponds to the [L] chain . [Weiman et al.,1984]

BINDING OF HP TO HAEMOGLOBIN [Hb]

Haptoglobin's primary function is to bind with haemoglobin in one-to-one ratio yielding a relatively high molecular weight complex that exceeds the kidney threshold for excretion [Lathem et al.,1960]. This prevents undue

loss of iron through urinary excretion and protects the kidney from damage by haemoglobin. [Ritche,1979].

The Hp-Hb complex is too large [molecular weight about 150,000] to pass through the glomerulus. Thus the level of circulating haptoglobin is the most important determinant of the apparent renal threshold [Laurell and Nyman,1957]. When the haptoglobin system is saturated , free [unbound] haemoglobin circulates briefly in plasma.

The hepatic parenchymal cells is partially responsible for the disposal of free haemoglobin. There is a low [0.2-0.6 g/L] renal threshold for free haemoglobin that is related to renal tubular reabsorption rather than to haptoglobin [Lathem et al.,1960]. Much of the haemoglobin appearing in the glomerular filtrate is reabsorbed in the proximal tubule. [Lathem et al.1960] . The rate of tubular reabsorption of haemoglobin in adult males is 1.43 ± 0.96/min. , if this capacity is exceeded, haemoglobin appears in urine. [Lowneistein et al.,1980].

Haptoglobin forms a stable irreversible complex with haemoglobin [Wejman et al.,1984]. [H] chain binds irreversibly to Hb. [L] chain does not bind Hb and will recombine with [H] chain Hb complex to form full Hp-Hb complex. [Valette et al.,1981]. Oxy-Hb, Met-Hb and carbon monoxy Hb

form complexes with Hp but desoxy-Hb and myoglobin do not.

As myoglobin does not combine with Hp, the haemoglobin binding capacity [HbBC] can therefore be used for differentiation between paroxysmal myoglobinuria and haemoglobinuria. [Javid et al.,1959].

SYNTHESIS AND CATABOLISM OF HAPTOGLOBIN

Haptoglobin is synthesized in the liver . [Merill,1964]. It is synthesized by hepatocytes in a precursor form , prohaptoglobin, which contains one alpha-subunit region and one beta-subunit region. Two of these molecules are joined by disulfide bond [Hanley and Heath,1985].

When haptoglobin is not bound to haemoglobin it leaves the plasms with half life - disappearance time of about five days. The haptoglobin-haemoglobin complex leaves much more rapidly with a halfife disappearance time of about nine minutes . About 50 tO 80% of the haptoglobin turnover in the normal subject is accounted for by the rapid pathway.[Nyman, 1959].

The hepatic parenchymal cell appears to be the main site of removal of the haptoglobin-haemoglobin complex. [Giblet, 1968].