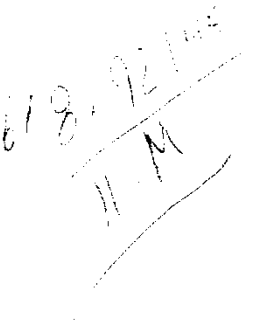
CHANGES IN SOME COAGULATION FACTORS (FACTOR IX & X) IN CHILDREN WITH NEPHROTIC SYNDROME



THESIS

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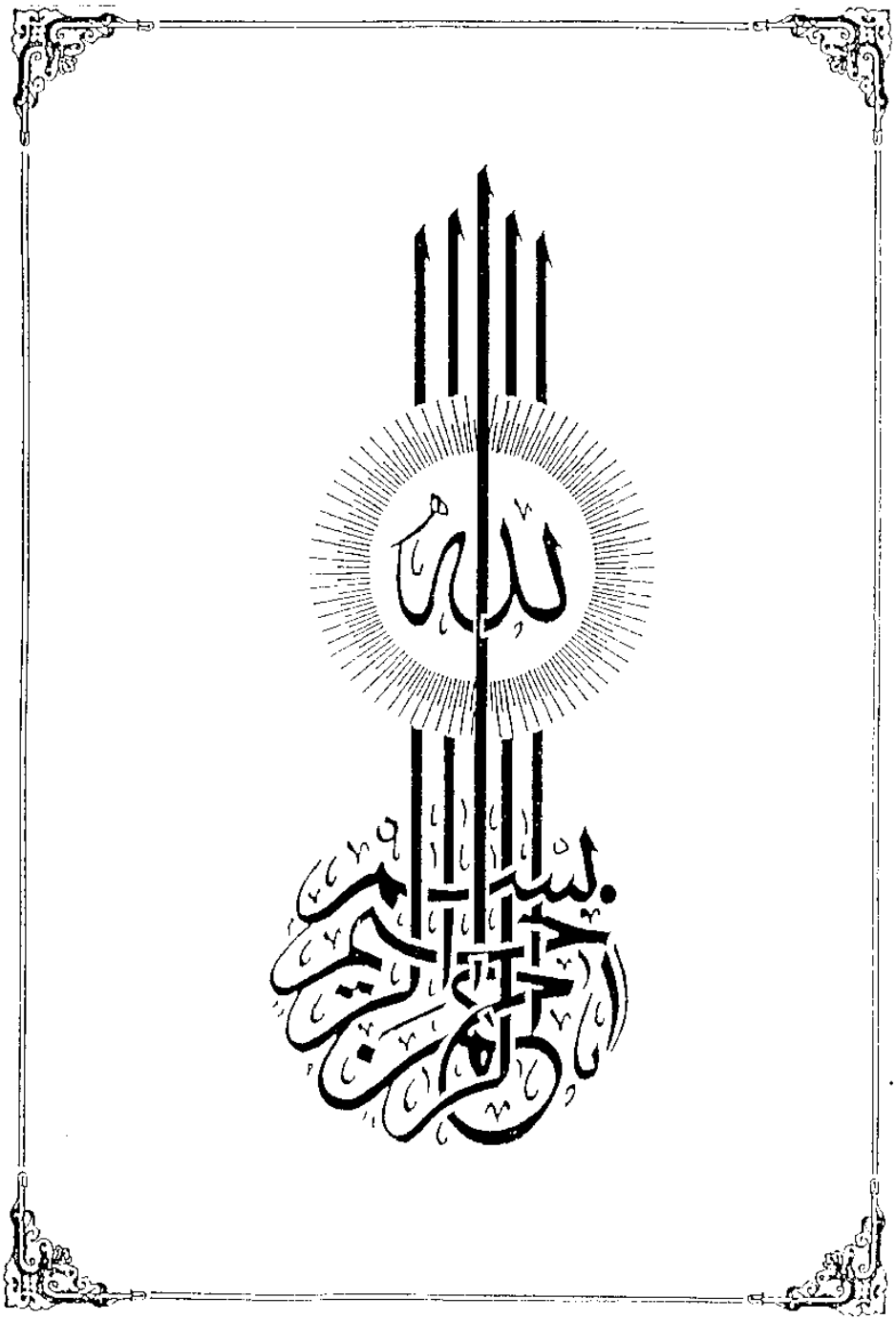

C O N T E N T S

1. INTRODUCTION

AIM OF THE WORK

I- Introduction and Aim of the Work

The term nephrotic syndrome has been adopted to describe the clinical picture caused by heavy urinary protein losses (Wrong, et al., 1979). It is characterized by generalized edema, hypoproteinemia, hyperlipidemia and excessive proteinuria.

The increased tendency to thrombosis in patients with nephrotic syndrome was first reported by Addis (1948). He commented on the high incidence of leg vein thrombosis, but it is now recognized that there is significantly higher incidence of both venous and arterial thrombosis (Thomson, et al., 1974).

Some aspects of blood coagulation in patients with nephrotic syndrome have previously been studied (Kanfer, et al., 1970, Kendall, et al., 1971) and a variety of coagulation abnormalities were found. Both increased and decreased plasma levels of various coagulation factors have been reported in this condition. Aquired factor IX deficiency in nephrotic syndrome was described by Handely & Lawrence, (1967), Natelson, et al., (1970), Koshy, et al,. (1975). Deficiency of factor VII and factor XII were also described by Epstein, et al., (1976) and Honig, et al., (1971) in nephrotic syndrome.

On the other hand Dossetor, et al., (1966) reported elevated platelet counts and increased levels of fibrinogen, factor VIII and factor VII - X complex. Vaziri, et al., (1980), also reported marked elevation of procoagulant activities of the coagulation factors IX, VIII, VII, X and V in the majority of tested patients with the nephrotic syndrome.

The Aim of the Work:

The aim of the present work is to study the changes in some of the coagulation factors (IX & X) in patients with the nephrotic syndrome before institution of any treatment.

These changes will be correlated with changes in serum albumin, 24 hours urinary protein excretion, serum cholesterol and serum creatinine levels in those patients, to search for any consistent abnormalities in the coagulation system of such patients which predispose to thrombotic episodes.

II. REVIEW OF LITERATURE

II- Review of Literature

1. Nephrotic Syndrome (NS)

A. Definition:

In the first half of this century the term "nephrosis" was introduced by Müller in 1905, and it was widely used in at least two quite different senses:

a) as a descriptive histopathologic term for renal disease without an iflamatory component and (b) to describe the clinical picture caused by heavy urinary protein losses. Much confusion was caused by this double use and so the word has been largerly abandoned.

By general agreement the term "nephrotic syndrome" has been adopted for the second of this meanings (Wrong, et al., 1979) Nephrotic syndrome is characterized by:

(a) Heavy proteinuria (in exess of 1 G /M^2/ day).

(b) Hypoalbuminemia (less than 2.5 G / deciliter).

(c) Edema.

(d) Hyperchclesterolemia (greater than 250 mg / deciliter).

(e) Haematuria, hypertension and renal insufficiency are additional findings in patients with more severe lesions in the kindey (White, 1971).

It may occur in the course of virtually many glomerular diseases and may be associated with a variety of extrarenal conditions (McIntosh, 1976).

B) Pathogenesis:

Proteinuria:

The excessive excretion of protein results from increased glomerular filtration of protein owing to increased permeability of the glomerular basement membrane (Drummond, 1979).

Sustained heavy proteinuria is often but not invariably accompanied by hypoalbuminemia (Glassock, et al., 1979). Urine losses of plasma proteins other than albumin are also of importance in NS.

Loss of antithrombin III (heparin cofactor) in the urine may be associated with increased coagulability, which may or may not be balanced by losses of procoagulant factors in the urine. If it is not balanced, it may produce a hypercoagulable state, and the increased tendency to thrombosis may lead to renal vein thrombosis (Glassock, et al.,1979).

Generally plasma proteins of low molecular weight such as albumin, Ig G and transferrin are excreted more readily in the NS than other proteins of large molecular weight such as lipoprteins. This relative clearnce of plasma proteins is in inverse relation to their size or molecular weight and is referred to

the selectivity of proteinuria (Drummond, 1979).

Hypoalbuminemia:

Hypoalbuminemia is caused by excessive urinary losses, increased renal catabolism and inadequate hepatic synthesis of albumin. Hypoalbuminemia results in decrease of plasma oncotic pressure which leads to disturbance in the Starling forces, acting across the peripheral capillaries (Glassock, et al., 1979). The plasma calcium concentration may be low as a consequence of the reduced albumin, since about half of the plasma calcium is bound to albumin , the concentration of ionized calcium, however remaines normal (Drummond, 1979).

Edema:

Edema (periorbital, peripheral, scrotal or abdominal) is the usual presenting complaint and may be massive (Cohn, 1976). The plasma protein level is not the absolute determination of edema of nephrotic syndrome, since rapid reversal of edema may occur without significant changes in the protein level.

There is in fact evidence of a complex disturbance

in body water with multiple factors playing a variable role in the maintainance of the syndrome.

The pathogenesis is related to:

1- Decrease in plasma oncotic pressure which leads to disturbance in the Starling forces acting across peripheral capillaries.

2- Intravascular fluid migrates into the interstitial tissue and causes edema particularly in areas of low tissue pressure.

3- These disturbances initiate a series of homeostatic adjustments designed to correct the resulting deficit in effective plasma volume.

4- These include activation of the renin-angiotensin-aldosteron system, enhanced antidiuretic hormone secretion, stimulation of the sympathatic nervous system and perhaps a reduction in the secretion of a postulated "natriuretic hormone".

5- These and other poorly understood adjustments lead to renal sodium and water retension because of avid reabsorption in distal nephron segments, resulting in unrelenting edema.

6- The severity of the edema correlates with the level of serum albumin and with the extent of urinary protein losses. (Glassock, et al.,1979).

Hyperlipidemia:

Most of the lipid fractions normaly found in plasma are elevated in the NS. There is a variable inverse relation between the degree of hyperlipidemia and the reduction in plasma albumin. The first explanation is that the lipoprteins are of relatively high molecular weight and consequently negligable amount is lost in the urine in comparison with that of albumin (Drummond, 1979). The second explanation is that the diminished plasma oncotic pressure also appears to stimulate hepatic lipoprotein synthesis. Low denisty lipoproteins and cholesterol are elevated most frequently but as the plasma oncotic pressure falls to very low levels, very low density lipoproteins, and triglycerides are also increased. The third explanation is that, exess urinary losses of plasma protein factors regulating lipoprotein synthesis or disposable may also contribute to the hyperlipidemic state.

C) Incidence:

There is geographical distribution in the incidence (Hendrickse, et al., 1963; Hutt, et al.,1964).

The incidence of new cases from birth to 16 years of age is about 2 per 100,000 population per year in

North America and is twice as high in males as females (Drummond, 1979).

It is more common than acute nephritis in tropical Africa (Hendrickse, et al.,1963; Hutt, et al., 1964).

It may occur at any age but it is commenst between 2 and 7 years of age (White, 1971). The minimal lesion accounts for 80 - 90% of cases of nephrotic syndrome in children, whereas in adults the figure is less than 20%.

D) Causes:

I- Primary glomerular diseases:

a. Minimal change disease.

b. Focal and segmental glomerulosclerosis and hyalinosis.

c. Membranous glomerulopathy.

d. Proliferative glomerulonephritis.

1- Membranoproliferative glomerulonephritis.

2- Cresentric glomerulonephritis.

3- "Pure" mesangial proliferative glomerulonephritis.

4- Focal and segmental proliferative glomerulonephritis.