PARATHYROID HORMONE IN NEPHROTIC SYNDROME IN CHILDREN

Thesis

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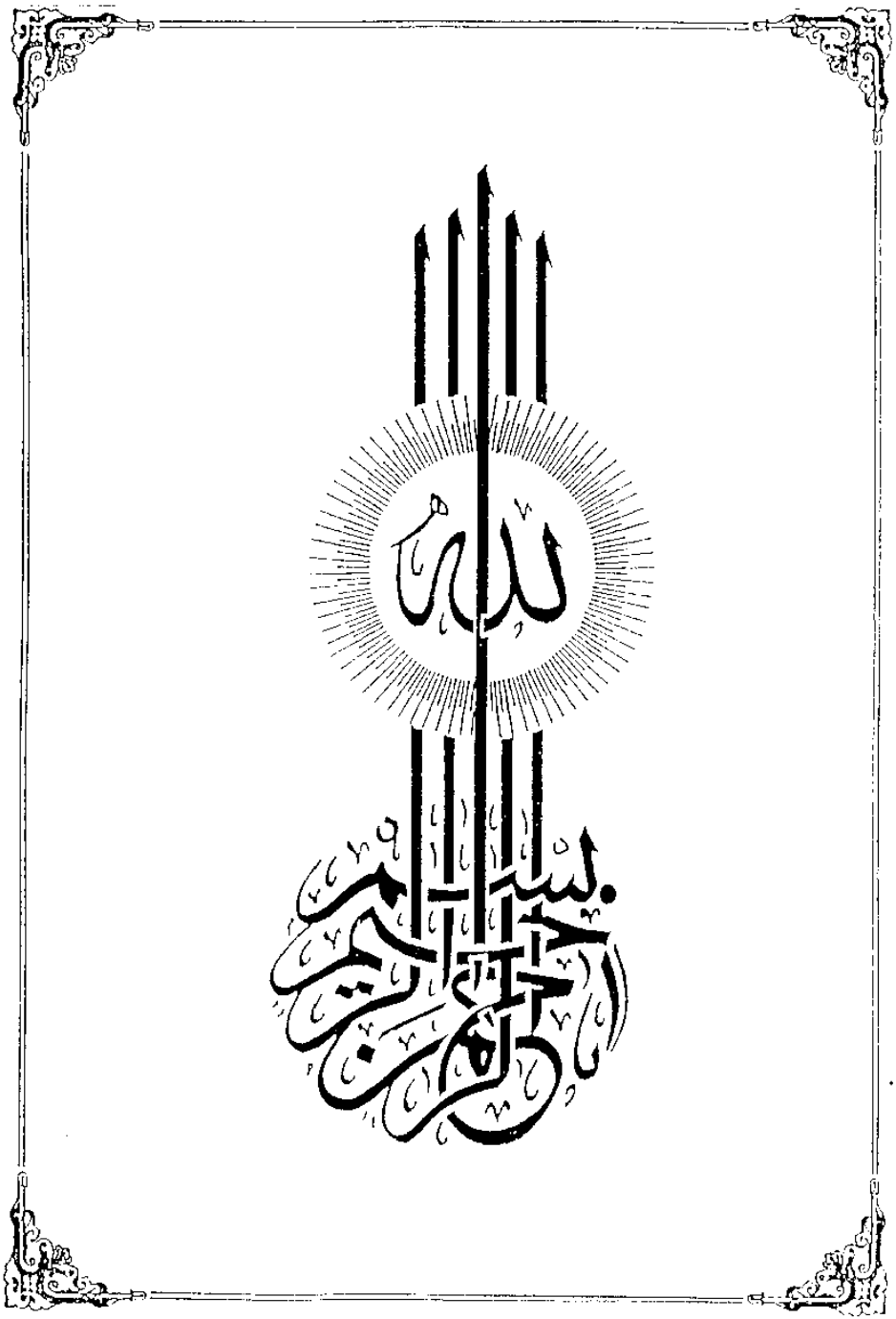

INTRODUCTION AND AIM OF THE WORK

The aim of this work is to study the functional state of the parathyroid glands and any changes in calcium and phosphorus metabolism in cases of nephrotic syndrome in children.

NEPHROTIC SYNDROME

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The nephrotic syndrome is defined as a clinical entity having multiple causes and characterized by increased glomerular permeability manifested by massive proteinuria (in excess of 3.5 gm/day/1.73 m^3 body surface area), hypoalbuminemia, hyperlipidemia and variable tendency towards edema *(Schreiner, 1971)*.

The nephrotic syndrome may present diagnostic difficulties as it is the more clinical manifestation of a large number of morphologically distinct glomerular diseases which in approximately ninety per cent of children result from primary glomerular diseases and in ten percent are secondary to systemic diseases. It can be present at any age including infancy *(Paul and Strife, 1982)*.

Causes of Nephrotic Syndrome in Children

I. *Idiopathic Nephrotic Syndrome*
- Minimal change nephropathy;
- Mesangial proliferation;
- Focal glomerulosclerosis;
- Immune complex glomerulo nephritis.
  . Membranoproliferative glomerulonephritis,
  . Acute poststreptococcal glomerulonephritis,
  . Membranous nephropathy;
- Congenital nephrosis.

II. *Systemic Causes*

- *Infections*: Syphilis, malaria;
- *Toxins*: Mercurials, bismuth, gold, probenicid, penicillamine;
- *Allergies*: Poison oak, bee sting, inhaled pollens, food allergy.
- *Cardiovascular*: Sickle cell disease, renal vein, thrombosis, congestive heart failure;
- *Malignancies*: Hodgkin's disease, leukemia, carcinoma,
- *Other*: Amyloidosis, systemic lupus erythromatosis, anaphylactoid purpura.

(Paul and Strife, 1982).

Clinical and Laboratory Abnormalities

1. *Proteinuria*

It is a constant feature in nephrotic syndrome, the amount of protein in urine is usually very large varying from 3-13 gm/L.

Proteinuria arising from defect in glomerular permeability can result from abnormalities in charge-selective or size-selective barrier or both *(Cotran and Rennke, 1983)*. Predominantly charge-selective barrier defects arise from diffuse biochemical changes in glomerular structure usually unassociated with optically recognizable abnormalities, whereas the size-selective barrier defects are usually associated with optically recognizable abnormalities of glomerular structure. Heavy proteinuria can and does arise

when only a small percentage of the total filtering surface area develops a size-selective barrier defect characterized by abnormally large defective pore radius *(Brenner et al., 1978)*.

Protein excretion rates in nephrotic syndrome are influenced considerably by both glomerular filtration rate and the plasma albumin concentration. A dramatic fall in plasma albumin might lead to a reduction in the urinary excretion of albumin even though the fundamental defect in glomerular capillary wall function remains unaltered. For this reason, it has been suggested that protein excretion rates should be represented as clearance rates for specific proteins, or as clearance ratios, e.g., clearance of albumin/clearance of creatinine. The advantage of this measurement is that urine collections need not be timed. Expression of protein concentration/ creatinine concentration in untimed urine specimens is another way to avoid the necessity of collection of a 24 hour urine. If this ratio exceeds 3.5 it usually indicates nephrotic range proteinuria *(Show et al., 1983)*.

In proteinuria of glomerular origin, a number of plasma proteins are found, and several authors have suggested that determination of the fractional clearance of excreted protein as a function of their molecular size is an indirect estimate of the extent of the glomerular capillary wall damage. Measurement of IgG clearance has been used to assess the

severity of the size-selective barrier defect of glomerular permeability. An isolated increase in fractional albumin clearance would be indicative of a defect in the charge-selective barrier *(Myers et al., 1982)*.

Transient elevations of plasma albumin by infusion of concentrated albumin in nephrotic patients markedly increase albumin excretion rates, similar increase also follows expansion of plasma volume with isotonic dextran *(Richard et al., 1986)*.

As a result of protein loss and increased catabolic activity, hypoproteinemia develops and is a diagnostic feature of the nephrotic syndrome.

2. *Hypoalbuminemia*

There is an approximate correlation between the degree of proteinuria and the extent of hypoalbuminemia. Absolute hepatic albumin synthesis is usually modestly increased but may be normal or even decreased whereas fractional albumin catabolism is increased in most but not all patients. A substantial fraction of albumin catabolism occurs in the kidney in proteinuric states, and the total external catabolism is decreased in proportion to the declining serum albumin concentration. The interstitial albumin concentration falls to a greater extent than plasma albumin, and the ratio of intravascular to extravascular (interstitial) albumin mass rises from normal values of about 0.8 to values in excess of 1.1 *(Bernard, 1982)*.

Increased dietary intake of protein in nephrotic states leads to an increase in the urinary protein excretion and no or rather modest increase in plasma albumin, except when severe malnutrition is present. Restriction of protein intake in nephrotic states is followed by a reduction in urinary protein excretion and little or no change in plasma albumin level *(Kaysen et al., 1984)*.

The availability of drug binding sites may be restricted by hypoalbuminemia and leads to high levels of free drug, enhancing the potential for toxic reactions *(Richard et al., 1986)*.

Other Plasma Proteins

In addition to the well recognized deficiency of albumin, other plasma proteins may have altered serum or plasma concentrations, serum level of alpha-2 and beta globulin are increased, alpha-1 globulin may be normal or reduced. IgG levels may be significantly decreased, whereas IgM, IgA, or IgE levels usually are normal or even elevated. The changes in Ig levels seem to depend on the nature of the underlying lesion *(Slager et al., 1978)*. There may be an increase in fibrinogen levels and an elevation of the levels of factors V, VII, VIII and X, which are mildly increased *(Vaziri, 1983)*. Antithrombin III (Heparin cofactor) levels may be normal or greatly reduced, especially with severe hypoalbuminemia, accelerated thromboplastin generation and increased platelet aggregation has been noted. Elevated B-

thromboglobulin levels may be a sign of underlying spontaneous thrombosis *(Adler et al., 1980)*. Factors IX and XII may be depressed in nephrotic syndrome in part due to excessive urinary loss . Antiplasmin, - antitrypsin levels, plasminogen activator, and endothelial prostacyclin-estimulating factors may be decreased. These findings may contribute to the well-recognized tendency to spontaneous thrombosis observed in patients with nephrotic syndrome *(Vaziri et al., 1982)*.

Urinary loss of proteins having important metal or hormone-binding functions may contribute to associated clinical findings. Serum levels of T_4 and T_3 are decreased mainly due to binding of these hormones to thyroxine binding protein (TBG) *(Afrasiabi et al., 1979)*.

Loss of cholecalciferol-binding globulin may result in an acquired vitamin D deficiency state with low plasma levels of 25-hydroxycholecalciferol *(Barragry et al., 1977)*.

3. *Hyperlipidemia and Lipiduria*

Hyperlipidemia and lipiduria are common in patients with nephrotic syndrome. The characteristic changes in serum lipids of these patients include a rise in the level of both low density and very low density lipoproteins. The former is the major carrier of cholesterol and the latter of triglycerides, thus, the serum levels of both cholesterol and triglycerides are elevated *(Baxter, 1962)*. High density lipoprotein may be normal, increased or reduced depending on

the severity of proteinuria and the nature of the underlying lesion and permeability defect *(Newmark et al., 1975)*.

The mechanisms which underly the disturbance in lipid metabolism are well understood. Currently available data suggest that reduced plasma oncotic pressure from hypoalbuminemia and/or decrease in plasma viscosity results in enhanced hepatic production of very low density lipoprotein and interferes with the peripheral utilization and/or catabolism of lipoprotein *(Yedgar et al., 1985)*.

Lipiduria is chiefly manifested by the presence in the urine of double refractile lipid bodies containing cholesterol esters and/or fat-filled casts. These are signs of the disordered lipid metabolism and possibly the excessive filtration of lower molecular weight high density lipoprotein *(Show et al., 1983)*.

4. *Edema*

Edema is the sign that dominates the clinical pattern, it is the most variable cardinal feature of the nephrotic syndrome. It is a secondary manifestation that is influenced by a number of factors other than hypoproteinemia, such as fluid and salt intake.

The mechanism of the formation of edema is complex; some of the factors are: (1) reduction in plasma colloid osmotic pressure consequent to decreased concentration of serum albumin; this is responsible for a shift of extracellular

fluid from the intravascular to the interstitial compartment with edema formation; (2) marked reduction in the urinary excretion of sodium due to an increase in tubular reabsorption; and (3) retention of water which may result from inappropriate release of an antidiuretic hormone in response to concentration of the intravascular volume. It is also possible that a net increase in sodium reabsorption in the proximal tubule, together with passive reabsorption of water along an osmotic gradient in this segment, reduce the volume of the filtrate delivered to the ascending limb of the loop of henle and to the distal convoluted tubule for formation of dilute urine. In such a situation, ingestion of excess water could lead to fluid retention and progressive decrease in serum sodium level and plasma osmolality *(Nelson, 1984)*.

Idiopathic Nephrotic Syndrome (INS)

It is a clinical pathological entity, in which the nephrotic syndrome develops in the absence of any underlying heredofamilial or multisystem disease or drug or microbial exposure. Prior to the introduction of percutaneous renal biopsy, this group of disorderswas was usually regarded as a single disease entity having a common etiology and pathogenesis. It is now possible to classify idiopathic nephrotic syndrome into several reasonably well-defined groups of clinical-pathological entities *(Richard et al., 1986)*.

Prospective epidemiologic studies in children with the nephrotic syndrome, conducted by the International Study of Kidney Disease in Children (ISKDC), have permitted development of predictive formulas that make possible a more accurate prebiopsy identification of the underlying primary glomerular lesions. These formulas are based on a multivariant analysis of clinical characteristics of well defined, unselected populations of nephrotic children, including age, sex, blood pressure, urinalysis, C_3 level serum creatinine, serum albumin and selectivity of proteinuria. Such multivariant analysis have been less successful in adults in the development of prebiopsy predictions *(ISKDC, 1978)*. In children. these predictive criteria are of greater use in enhancing the diagnostic, so as to lead to an early renal biopsy and delay in glucocorticoid therapy until the true nature of the lesion is documented *(ISKDC, 1982)*.

Minimal Change Disease (MGL)

Minimal change nephrotic syndrome is the form of primary nephrotic syndrome characterized by the absence of major structural glomerular change. One of the characteristic features of minimal change lesion is its predilection to affect young children between the age of 2 and 6 years *(Grupe, 1982)*. Minimal change lesions account for 76% of the cases of idiopathic nephrotic syndrome due to primary glomerular disease in children, and are found in over 85% of