IRON CHANGES IN NEPHROTIC SYNDROME

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THESIS

SUBMITTED FOR THE PARTIAL FULFILMENT

OF MASTER DEGREE IN

(PEDIATRICS)

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1987

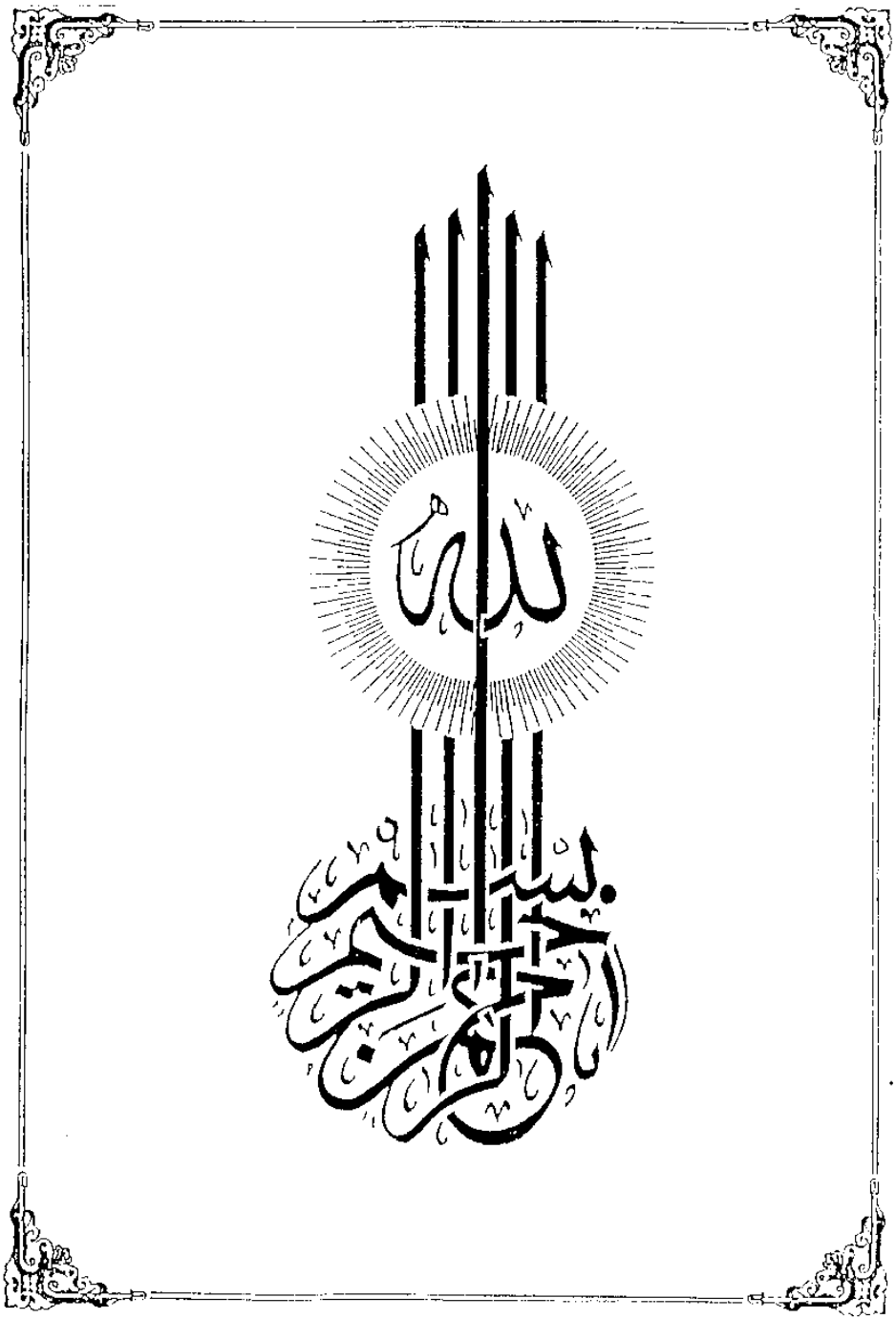
A C K N O W L E D G E M E N T

I would like very much to seize this special opportunity to express my deepest appreciation and greatest gratitude to Prof. Dr. Farida Farid, Assist. Prof. of Pediatrics for her thankful supervision and precious advices she has extended to me during my work.

I'm also greatly overwhelmed by the constant help offered by Prof. Dr. Fadila Sabry, Assist. Prof. of Clinical Pathology .

I'm also ultimately thankful to Dr. Nagia Bahgat, Lect. of Pediatrics, for her continuous assistance she has given me throughout the course of this work.

I'm again thankful to Dr. Mostafa El Bassad, Lect. of Biochemistry, for his assistance.



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INTRODUCTION AND AIM OF THE WORK

Iron deficiency anemia had been reported in patients with nephrotic syndrome, and this was attributed to excessive urinary losses of transferrin and iron. (Rifkind et al., 1961, Hancock et al., 1976, Ellis, 1977, and Brown et al., 1984.).

Other investigators had doubted whether the anemia could be produced by the relative small iron loss in urine. (Wiltink et al., 1972).

The aim of our work is to study iron changes in nephrotic syndrome by estimating :serum iron, total iron binding capacity (TIBC), and urinary iron loss in order to clarify the possible impact of urinary iron loss and iron-binding protein as a cause of anemia in nephrotic syndrome.

All patients have been selected at the stage of proteinuria.

N E P H R O T I C S Y N D R O M E

A- Definition :

Schreiner (1971), defined the nephrotic syndrome as a " clinical entity having multiple causes and characterized by increased glomerular permeability manifested by massive proteinuria. There is variable tendency towards edema, hypoalbuminemia, and hyperlipidemia. Protein excretion rates are usually in excess of 3.5 gram/ day/ 1.73 m^2 body surface area in the absence of a depressed glomerular filtration rate (G F R)".

B- Types of nephrotic syndrome :

1- Idiopathic nephrotic syndrome (I N S).

2- Congenital nephrotic syndrome (C N).

3- Familial nephrotic syndrome.

4- Nephrotic syndrome associated with specific etiological events or in which glomerular disease arises as a complication of other diseases.

1- Idiopathic nephrotic syndrome :

It is now possible to classify I N S into several reasonably well defined groups of clinical-pathological entities (Heptinstall, 1983) :

a- minimal change disease
b- mesangial proliferative glomerulonephritis
c- focal glomerular sclerosis
d- diffuse glomerular sclerosis
e- membranous glomerulonephritis
f- mesangiocapillary glomerulonephritis
g- endocapillary proliferative glomerulonephritits

" Minimal change disease "

Munk, 1946 coined the term lipoid nephrosis to describe a group of patients with heavy proteinuria unaccompanied by abnormalities of glomeruli examined by light microscopy. (Munk, 1946).

Prominent lesions consisting of lipid droplets in the cells of the proximal tubules were noted. This suggested that proteinuria might be the result of defective reabsorption of normally filtered protein. However, more careful biopsy material revealed a lesion of the glomerular epithelial cells consisting of juxtaposition of the normal club-shaped foot processes and obliteration of the slit-pore membrane

complex. (Farquhar et al., 1957).

The term lipoid nephrosis has now fallen into disuse. The terms : minimal change lesion, minimal change disease or minimal change nephropathy have become more widely used instead.

-Etiology of minimal change disease :

a- Unknown.

b- Idiopathic.

c- Genetic or familial.

d- Atopy.

e- T cell dysfunction :

In 1974 Shalhoub developed the following theory " lipoid nephrosis is a systemic disorder of cell mediated immunity in which episodic or sustained domination of the immune system by a clone of T cells results in the production of a circulating lymphokine toxic to the glomerular basement membrane (G B M). This lymphokine, tentatively named basement membrane toxin, augments the permeability of G B M to protein".

In a study done by Mehta et al (1988), dysfunction of cell mediated immunity was reported as evidenced by:

- low absolute lymphocyte count,
- depressed blastogenesis,

-poor skin reactivity to dinitrochlorobenzene,
-low serum Ig G concentrations while the Ig A, Ig M, and C_3 concentrations were normal.
But they did not establish whether the depression in cell mediated immunity is a primary event or secondary to the hypoalbuminemia, hyperlipidemia or zinc deficiency that co-exists in these patients. It has been postulated that an abnormal immunogenic response to some unknown stimuli may be a primary event, leading to suppression of T cell functions. This may lead to depressed cell mediated immunity as well as impairment of T cell dependent B cell activation accounting for the low concentrations of Ig G in these patients. This same deviated immune response may be resposible for the production of an abnormal lymphokine with properties of increasing vascular permeability.

2- Congenital nephrotic syndrome :

The onset of nephrotic syndrome at birth, in the neonatal period, or in the first month of life has been reffered to as the " congenital nephrotic syndrome " (Lemire and Kaplan, 1985).

Mahan et al., in 1984 described congenital nephrotic syndrome in the first 3 months of age, pathologic features of which were thought to be of the Finnish

type (it was called Finnish type due to relative frequent occurrence of this syndrome in Finland).

Bensman and Sinnassamy (1985), mentioned (CN) at 3 weeks patient and another 7 weeks patient, pathologic findings resembled that noted in minimal change disease. Despite the very young age of the patients, good results of steroid therapy were obtained after 6 and 8 weeks of treatment with no relapse.

However, Mahan et al., (1984) reported that the overwhelming majority of infants with onset of (CN) in the first 3 months are found to have steroid unresponsive disorder.

Death in the first year of life is usually secondary to infection. The normal infant is immunologically immature particularly at 3 to 4 months of age when the passively acquired maternal Ig G disappears. In addition to losses of Igs in the urine, Ig production is depressed in many infants with nephrotic syndrome and this accentuates their vulnerability to infection. Replacement therapy with Igs is therefore recommended.
(Lemire and Kaplan, 1985).

3- Familial nephrotic syndrome :

In 1951, Fanconi described what he considered to be a distinct form of "familial" nephrotic syndrome of childhood characterized by :

- occurrence of the disease in multiple siblings and
- onset after infancy.

Norio (1969) reported cases of nephrotic syndrome found in concordant twins (both affected), in sibling pairs and in nephrotic patients with close relatives who were nephrotics.

Roy and Pitcock (1971) reported affected monozygotic twins and suggested that when monozygotic twins are affected, the clinical courses and biopsies are similar.

Bader et al., (1974), contrary to the previous reports, reported that in their experience, patients with familial idiopathic nephrotic syndrome cannot be reliably distinguished from patients with sporadic idiopathic nephrotic syndrome on clinical or histologic grounds. They found that renal histopathology in those with both the familial and sporadic forms of the disease was most often that of minimal glomerular changes. They added that they did not note an increased severity or worse prognosis in children with the familial form of the disease.

Also, contrary to previous investigators, they found that identical twins had significantly different clinical and histopathologic findings i.e one had minimal glomerular changes, and the other had major glomerular changes and sclerotic glomeruli.
They added that the genetic relationship is not the only explanation for a familial aggregation of the disease and that an unidentified environmental factor that is correlated with socioeconomic status may play an important role in the etiology.

4- Nephrotic syndrome associated with specific etiological events or arises as a complication of other diseases :

a- Medications

mercury, organic gold, penicillamine, probenecid, captopril, nonsteroidal anti-inflammatory agents, lithium, rifampicin, mesantoin, tolbutamide, bismuth.

b- Allergens, venoms, immunizations

bee sting, pollens, antitoxins (serum sickness), snake venom, diphtheria toxoid, pertussis, tetanus toxoid, vaccines.

c- Infections

poststreptococcal glomerulonephritis, infective endocarditis, leprosy, syphilis, tuberculosis,

chronic bacterial pyelonephritis with vesico-ureteral reflux.

Hepatitis B, cytomegalovirus, infectious mononucleosis (Epstein-Barr virus), herpes zoster, vaccinia, acquired immunodeficiency syndrome.

Malaria (especially quartan malaria), toxoplasmosis, Schistosomiasis, filariasis.

d- Neoplastic

carcinoma, sarcoma, Hodgkin's disease, chronic lymphatic leukemia

e- Multisystem disease

systemic lupus, dermatomyositis, rheumatoid arthritis, Good pasteur's syndrome, Schonlein-Henoch purpura, polyarteritis, sarcoidosis, ulcerative colitis, amyloidosis.

f- Heredofamilial and Metabolic

hereditary diabetes mellitus, myxedema, hyper-thyroidism, amyloidosis, Alport's syndrome, Fabry's disease, nail-patella syndrome, sickle cell disease, alpha$_1$-antitrypsin deficiency, congenital nephrotic syndrome, familial nephrotic syndrome.

g- Miscellaneous

malignant nephrosclerosis, unilateral renal arterial hypertension, intestinal lymphangiectasia, spherocytosis congenital heart disease, severe congestive heart

failure, constrictive pericarditis, tricuspid insufficiency, massive obesity.

C- Clinical criteria and pathogenesis of nephrotic syndrome :

One of the characteristic features of the minimal change lesion is its predilection to affect young children with a peak occurrence between the ages of 2 and 6 years.
The minimal change lesions account for 76% of cases of idiopathic nephrotic syndrome in children.
(Grupe, 1982).

Males predominate by about 2 : 1.
Viral upper respiratory infection is a common antecedent feature,
A back ground of allergy, atopy or recent immunizations may be found. (Meadow et al., 1981).

A full-blown nephrotic syndrome with : edema, heavy proteinuria, hypoalbuminemia and hyper lipidemia is the rule.

(a) Edema :

In many instances, the edema is a bothersome but not debilitating clinical feature, but occasionally it can be severe and associated with accumulation of peritoneal or pleural fluid. Pericardial effusions