THYROID FUNCTION IN ACUTE CHILDHOOD LEUKAEMIA

THESIS

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BY

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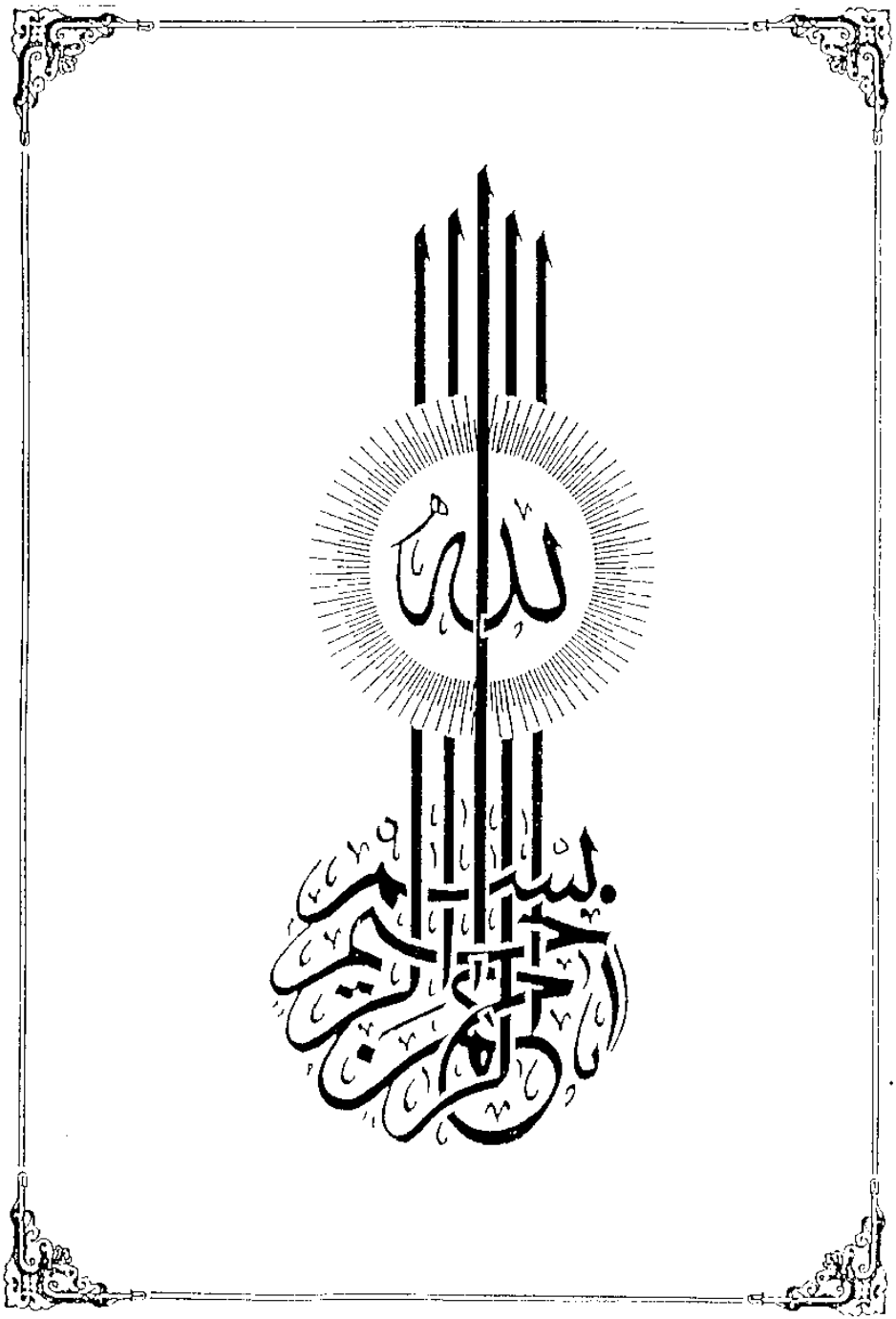

ABBREVIATIONS

ACTH : Adreno corticotrophic hormone .

ALL : Acute lymphoblastic leukaemia .

BMR : Basal metabolic rate .

CM : Condioned media .

CNS : Central nervous system .

DHCC : Dihydro cholicalciferol .

FSH : Follicle stimulating hormone .

G.H. : Growth hormone .

IGF : Insulin growth factor .

L.H. : Luteinizing hormone .

NGF : Nerve growth factor .

PBI : Protein bound iodine .

PTH : Parathyroid hormone .

PTU : Propyl thiouracil .

S.M : Somatomedin .

RIA : Radio immuno assay .

T_3 : Tri iodo thyronine .

T_4 : Tetra iodo thyronine (Thyroxine) .

TBG : Thyroxine binding globuline .

TBPA : Thyroxine binding prealbumin .

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INTRODUCTION AND AIM OF THE WORK

Retardation of growth has been observed in long survivor leukaemic children (Amadori, 1983). There was a degree of retardation in growth after prolonged period of anti- leukaemic therapy. (Badr, 1982). Also the skeletal maturity was markedly retarded specially with increased duration of the disease and/ or therapy. That degree of growth retardation could not be attributed to the disease itself. Prolonged chemotherapy and/ or irradiation may be responsible for that delay.

Children treated for acute leukaemia may be at substantial risk of growth hormone deficiency which is related to dose and fractionation of the irradiation (Shalet et al, 1976). Possible mechanisms of decreased growth hormone secretion include alteration in the secretion of the growth hormone releasing hormone, or release of the growth hormone itself or both.(Dickinson et al., 1978). The growth hormone deficiency and growth retardation become more manifest with increase in the duration of anti- leukaemic therapy.

In children treated for acute lymphoblastic leukaemia (ALL), there was an elevated basal thyroid stimulating hormone level (Shalet et al., 1977). Radiation induced damage to the hypothalamic - pituitary region is thought to be the cause of these abnormalities in growth hormone and in secretion of thyroid stimulating hormone.

The aim of the present work is to study thyroid functions in children affected with ALL and to follow up these functions after prolonged treatment with anti- leukaemic chemotherapy.

GROWTH AND DEVELOPMENT

Growth and development are often used interchangeably and in the normal child each parallels the other. The term growth means an increase in physical size of the whole or any of its parts. Development is used to indicate an increase in skill and complexity of function. Growth and development affected markedly by hereditary and enviromental factors prenataly and postnataly.

ROLE OF ENDOCRINE GLANDS IN NORMAL GROWTH AND DEVELOPMENT (Lowrey , 1973)

1- The pituitary gland :

It is well established that the influence upon the anterior pituitary is mediated by neurohumoral substances transported to the gland by the hypophysial portal system. During growth the histologic appearance of the anterior pituitary changes and very possibly reflects the changes in the products secreted by the gland. Six hormones are recognized as arising from the

anterior pituitary. These are: growth hormone, thyrotropin, corticotropin, prolactin and two gonadotropins. which are follicle - stimulating hormone (FSH) and luteinizing hormone (LH).

The normal physical growth of an individual depends upon an adequate secretion of the growth hormone and the genetic ability to respond. Growth hormone is present in the blood throughout all of the growing period and well into adult life. It may be in infancy than later, but there is no increase associated with the adolescent growth spurt. The growth hormone has its major influence on increasing the number of cells of the body from late infancy until adulthood. Growth hormone accelerate bone growth and tissue building.

2- The thyroid gland :

The thyroid gland is probably second only to the pituitary in relative importance in its influence on growth and development. There is active function of the thyroid gland during gestation, the absence or deficiency of thyroid secretion from late fetal life results in the clinical picture of cretinism, or in congenital myxedema. The results are stunted growth,

mental retardation, slowing of all metabolic functions and markedly retarded bone maturation. Thyroid hormone is actively secreted by the fetal gland and in its absence, there is a lack of brain growth probably both in cell number and in cell size. This is clinicaly apparent as microcephaly and retarded behavioral development. Following birth, the thyroid hormone influences both cell number and cell size. After infancy, the major effect appears to be on cell size rather than multiplication.

3-Adrenal glands :

The adrenal cortex produce three hormones :-

(1) Water electrolyte hormones, influence chiefly water, sodium and potassium balance.

(2) Corticoids which control carbohydrate, protein balance in the body. These hormones promote the catabolism and gluconeogenesis from protein. The use of large doses of corticoids in the treatment of various diseases in children has uniformly resulted in some retardation of growth, both in length and in weight.

(3) Androgens in their physiologic action they promote both musculinization and nitrogen retention.

4- Gonadal influences on growth and development.

The normally functioning gonads is necessary for proper development of the child. It is responsible for the development of the secondary sex characteristics.

5- The parathyroid gland :

It is responsible for normal bone development, which in turn is the limiting factor for statural growth. It regulates calcium and phosphorus metabolism in the body .

THE THYROID AND ITS EFFECT ON GROWTH

The thyroid hormones do not appear to play a significant role in the early growth and development of the human fetus, since even those with congenital aplasia of the thyroid gland are of normal size at birth (Underwood and Van Wijk 1981). Pickering and Fisher, (1958) showed that the major consequences of intrauterine thyroid deficiency in primate fetuses are retardation of osseous and the central nervous system development.

The critical period of thyroxine dependent brain growth extends from the last portion of gestation to several months postnataly. Hypothyroidism during this period results in markedly retarded growth of cell bodies, axons, and dendritic connections and delayed mylinization (Williams et al., 1981).

Although thyroid hormones may act directly on these processes, Walker and coworkers (1979) have demonstrated that the administration of thyroxine to mature mice significantly increases the brain concentration of nerve growth factor (NGF). These findings have raised the interesting possibility

that the effects of thyroxine on neural maturation may be mediated through NGF.

The importance of thyroid hormones for normal postnatal somatic growth is exemplified by the sever growth failure that regularly accompanies thyroid hormone deficiency (William R.D. ed.1981). Sever hypothyroidism cause nearly absolute growth arrest. Following correction of the thyroid hormone deficiency, growth is usually resumed at extra ordinarily rapid rates, a period of so called catch-up growth. The role of throxine on skeletal growth appears to be permissive one for the action of GH., since GH does not stimulate growth in hypothyroid animal (William 1981).

Froesh et al. (1976) said that triiodo-thyronine is necessary to obtain a maximal in vitro response of chick cartilage to a purified peptide belonging to the somatomedine family (NSILA).

Josef et al. (1981), said that there are several possible mechamicm by which thyroid hormone may affect cartilage growth ;-

1) direct stimulation of cartilage metabolism.
2) S.M stimulation by means of growth hormone release.
3) direct stimulation of S.M (for example induction of S.M production in liver.).
4) stimulation of other yet unknown serum factors affecting the cartilage.
5) more than one mechamism of thyroid hormome action on the cartilage.

Josef et al (1981). said that there is increase of serum SM activity in thyrotoxic patient and a fall in hypothyroidism and treated thyrotoxicosis give evidence that thyroid hormones are important regulators of S.M activity.

A mediating role for S M in the growth- promoting effects of thyroid hormones has been denied by Brommer et al. (1977). Similarly, Mosier et al. (1977) did not find any significant fall of S M in propyl thiouracil (PTU) treated rats and claimed that PTU induced hypothyroidism resulted in a disturbance of the intrinsic cartilage function.

Burstein et al. (1979) observed a decrease of insulin like factor which seems to be similar or identical with somatomedins (Zapt et al., 1978). and its carier protein in PTU treated infant and newborn rats. The decline of insulin- like factor was preceded by that of growth hormone which supp-orts the hypothesis that thyroid hormones stimulate SM. via the growth hormone. Furlanetto et al. (1979) reported reduced immuno-reactive SM concentration in the serum of patients with primary hypoglycaemia.

Thyroid hormone also appears to infleunce the growth at the pituitary level regulating the syn - thesis and secretion of G.H. Furlanetto et al (1979) said that hypothyroid patients frequently have severly blunted G.H. responses to a variety of provacative stimuli and , perhaps, for this rea-son, their serum somato-medin levels are someti-mes low .

Samuels et al. (1979) and Coworker have carried out extensive studies on the effect of thyroid hormone on the induction of the m. RNA for G.H.