Prevalence of Thyroid Autoantibodies in Down Syndrome

Thesis
Submitted for the partial fulfilment of M.Sc. degree in Paediatrics

By Maha Mohamed Ahmed Awadalla
M.B.Bch- Ain Shams University

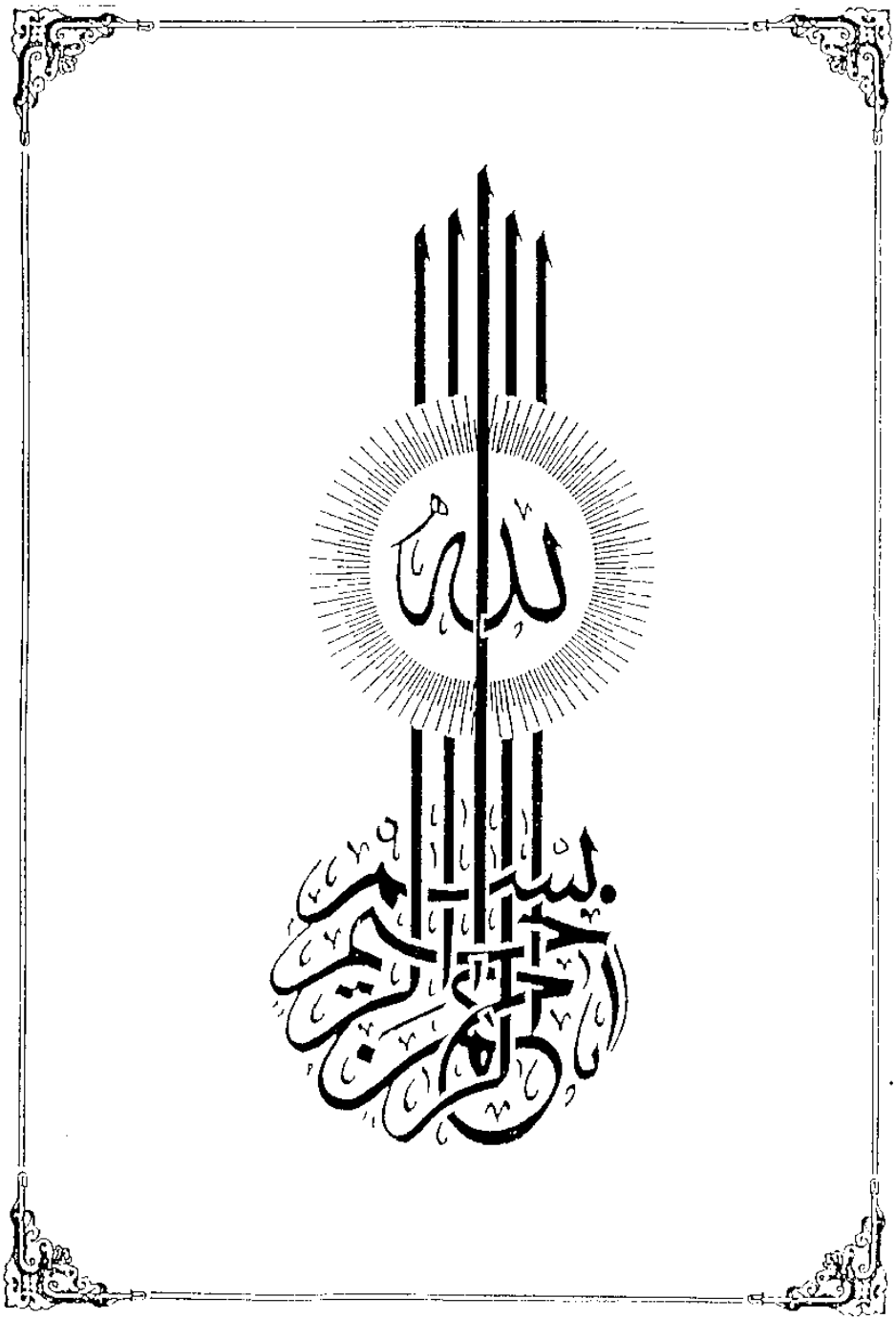
Under supervision of

Prof. Dr.
Rabah Mohamed Shawky
Professor of Paediatrics and Genetics
Head of Genetics Unit
Faculty of Medicine. Ain Shams University

Dr.
Heba Hassan El Sedfy
Ass. Prof of Paediatrics
Faculty of Medicine
Ain Shams University

Dr
Hanaa A. H. Amer
Lecturer of Clinical Pathology
Ain Shams University

1998



ACKNOWLEDGEMENT

- I would like to express my sincere deepest thanks and gratitude to **Professor Dr. Rabah Mohamed Shawky**, Professor of Paediatrics and Head of Genetics Unit, Faculty of Medicine, Ain-Shams University, for her help and guidance which together have enabled me to accomplish this work under her supervision.
- I would also like to express my heartful gratitude and thanks to **Dr. Heba Hassan**, Assist. Professor of Paediatrics, Faculty of Medicine, Ain-Shams University, for her valuable assistance, encouragement, and continuos guidance.
- I Would also like to express my thanks to **Dr. Hanaa Amer**, lecturer of Clinical Pathology Faculty of Medicine, Ain-Shams University, for her masterly help and great kindness by which the completion of this work became possible.

LIST OF CONTENTS

	page
1. Introduction and aim of work--------	1
2. Review of literature----------	3
Down syndrome	
' Historic prospective.	3
' Incidence of Down syndrome	4
' Etiology of Down syndrome	5
' Types and cytogenetics	8
' Clinical features	13
' Malformations and complications	19
' Dermatoglyphics	28
' Prognosis	30
' Risk of recurrence & genetic counseling	30
' Prenatal diagnosis	32
Autoimunity	35
' Spectrum of autoimmune diseases	37
' Thyroid antigens	40
' Thyroid antibodies	41
Association between Down syndrome and autoimmune thyroid disease.	44
Subclinical hypothyroidism	49
3. Patients and methods----------	51
4. Results----------	54
5. Discussion----------	70
6. Recommendation----------	79
7. Summary & conclusion----------	80
8. References----------	83
9. Arabic summary----------	

LIST OF ABBREVIATIONS

AFP	Alpha fetoprotein
ALL	Acute lymphoblastic leukemia
AMA	Antimicrosomal antibody
AML	Acute myeloid leukemia
ATA	Antithyroid antibodies
B-HCG	Beta subunit of human chorionic gonadotropin
C.P	Cerebral palsy
D.S	Down syndrome
ECHO	Echocardiography
EEG	Electroencephalography
ELISA	Enzyme-linked immunoabsorbent assay
HDR	Human leukocytic antigen D-related type
Ig	Immunoglobulins
IVP	Intravenous pyelogram
L-thyroxine	Levo thyroxine
MIU	Microinternational unit
PAPP-A	Pregnancy associated plasma protein A.
q	Long arm of any chromosome
S.H	Subclinical hypothyroidism
SD	Standard deviation
SLE	Systemic lupus erythematosis
t	Translocation
T_4	Thyroxine
TSH	Thyroid stimulating hormone

Introduction and aim of work

Down syndrome (trisomy 21) is the 2nd commonest serious birth defect, after neural tube defects and is the commonest survivable chromosomal abnormality ***(Kennedy et al., 1992).***

Growth in patients with Down syndrome is reduced specifically between age of one year to three years, so that it reaches –3 SD (***Piro et al., 1990***).

The similarity between the features of Down syndrome and hypothyroidism has long been recognised and has the potential benefit of thyroid hormone treatment ***(Kennedy et al., 1992***).

Neonatal hypothyroidism is well described in Down syndrome patients with incidence of 1:141 compared to 1:3800 in the general population i.e.28 times more in Down patients than in the general population ***(Fort et al., 1984, Cutler et al., 1986***).

An association between autoimmune thyroid dysfunction and Down syndrome is widely recognised, the overall incidence ranges from 2% to 63% (***Friedman et al., 1989***).

Acquired autoimmune thyroid disease is common and often occurs prematurely; hyperthyroidism and more particularly hypothyroidism are well recognised to occur with

increased frequency in Down syndrome patients, hence prompt recognition and treatment of these disorders are important for the physical well being and mental development of these patients ***(Kennedy et al., 1992)***.

In a study done by ***Rubello et al., (1995)*** thyroid dysfunction has been reported with high prevalence in Down syndrome patients; both hypo- and hyperthyroidism has been documented in these patients but the most frequently observed condition appeared to be subclinical hypothyroidism.

Aim of work:

In this study the prevalence of anti-microsomal antibodies in a group of Down syndrome patients will be determined and compared to their prevalence in a group of healthy children. The role of anti-microsomal antibodies in thyroid dysfunction in Down syndrome will also be studied.

Down syndrome

Historic perspective

21.Trisomy was the first chromosomal aberration to be described in man. It is the most frequent autosomal anomaly, ***(Le jeune et al., 1959)***. The first clinical description of the disease appeared by ***Edward Seguin, who in 1846*** used the name "furfuraceous idiocy". In *1866, Langdon Down* redescribed this group of mentally retarded children among whom he recognised great resemblance to certain oriental appearance, as Mongolian idiocy or mongolism. This term "Mongolism" has been justifiably criticised, particularly for its racial implications, ***(Novitski, 1982)***.

Polani et al in 1960 described translocation Down syndrome. ***Clark et al., 1961*** discovered mosaicism for an extra G group chromosome. Anglo-Saxon authors most frequently designate this disease by the term Down syndrome; other authors prefer the more precise term, 21 trisomy, ***(Grouchy&Turleau, 1984)***.

Incidence of Down syndrome

The incidence of 21 trisomy is 1.45/1000 or about 1 for every 700 births. The sex ratio is approximately 3 males to 2 females. 95% of cases of trisomy are caused by non-disjunction whereas translocation or mosaics are responsible for 5% of cases. Non disjunction causing trisomy 21 originates in the ova in 95% of cases and in the sperms in 5% of cases ***(Antonarakis, 1991)***.

The prevalence of Down Syndrome in the Genetics clinic, Children's Hospital Ain Shams University in the period from 1990-1995 was estimated to be 1/1000 ***(Shawky et al., 1997)***.

Aetiology

There are many factors contributing to the occurrence of Down syndrome.

Maternal age:

It is a well known etiological factor. The risk of a child being born with trisomy 21 increases exponentially with maternal age. It was shown to be 1 per 2000 at 20 years, increasing slightly at the age of 30 yrs; it is about 1 per 300 at the age of 35 yrs, 1 per 100 between 40-45 yrs and attains 1 per 50 at the age of 45 yrs, ***(Penrose, 1933, Lilienfield&Benesch, 1969, Mikkelsen, 1972, Kornafel&Saucer, 1994)***. Hence it is evident that non disjunction is heavily influenced by maternal age as the risk increases 6.5 times at the age of 35-40years and 20 folds at the age 40-45years over that of 20-24years old females (***Stoll et al., 1993***). The distribution curve of maternal age shows two peaks; one peak near the age of 28 yrs, the other near 36-37yrs. The first corresponds to the maximum peak for births and includes the majority of sporadic cases or inherited translocations. The second peak seems strongly correlated to maternal age, ***(Grouchy&Turleau, 1984)***. It was suggested that the rate of Down syndrome increases rapidly with maternal age approximately 30% per year after 30yrs, ***(Hook, 1978)***. A high correlation exists between increasing maternal age and non-disjunction resulting in the presence of extra chromosome, ***(Cohen&Nadler, 1983)***. Many mechanisms have been suggested such as delayed fertilisation and ageing of the ovum but non are entirely convincing, ***(Grouchy&Turleau, 1983)***.

Paternal age:

Bennet&Abroms, (1979), suggested that the significant paternal input in Down syndrome may explain some data that have been overshadowed by the strength of the maternal age effect, they also suggested that the paternal age is more likely to be responsible for the seasonal and geographical fluctuation because the male germ tissues were more susceptible to changes in the environmental conditions than that of female germ tissues. Spermatogonia undergo successive mitosis throughout an adult life with continuous differentiation into spermatocytes. Meiosis among spermatocytes is continuous throughout an adult life, ***(Bishop&Walton, 1956)***. Thus at any given time in an adult life there will be a population of spermatogonia, primary, secondary spermatocytes and spermatides at varying stages of division and maturation. One might expect that these cells would be differentially susceptible to the action of environmental mutagens such as viruses, radiations and chemical pollutants, ***(Bennet&Abroms, 1979)***.

Spermatocide use: ***Jick et al., (1981)*** reported a great prevalence at birth of Down syndrome and other congenital anomalies (limb anomalies, neoplasms and hypospadias) among children of women who had used spermicides during the 10 months before conception. A connection also had been suggested between the use of vaginal spermicides and occurrence of Down syndrome among offspring born to women who used these contraceptive agents, ***(Kenneth&Rothman, 1982).***