EVALUATION OF PRIMARY HUMORAL IMMUNODEFICIENCY IN CHILDHOOD LYMPHOMA

Thesis

*Submitted for the partial fulfillment of the Master Degree in **Pediatrics***

By

Shaimaa Hassan Ramadan Hassan
(M.B., B.Ch, 2004)
Faculty of Medicine – Ain Shams University

Supervised by

Prof. Shereen Medhat Reda

Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. Hanaa Mohamed El-Sayed Afifi

Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Dr. Iman Ahmed Ragab
Lecturer of Pediatrics
Faculty of Medicine - Ain Shams University

Ain Shams University
Faculty of Medicine
2009

ACKNOWLEDGEMENT

First and foremost thanks to **ALLAH** *to whom I relate any success in achieving any work in my life.*

I would like to express my deepest appreciation and gratitude to Prof. Dr. Shereen Medhat Reda, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for suggesting and planning this study. Her keen supervision, continuous guidance, experienced advice. No words can express my deepest gratitude for her overwhelming kindness and encouragement.

My sincere thanks to Prof. Dr. Hanaa Mohamed El-Sayed Afifi, professor of clinical Pathology, Faculty of Medicine, Ain Shams University, for her great effort, constructive advice and valuable guidance throughout work.

I would like also to thank Prof. Dr. Azza Abdel Gawad Tantawy, Professor of Pediatrics, Faculty of Medicine, Ain Shams University for her continuous guidance, experienced advice and her great effort throughout work.

I am also very grateful to Dr. Iman Ahmed Ragab, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University for her co-operation, valuable comments, generous help, and her great effort throughout work.

I also appreciate so much the sincere help and cooperation of Prof. Dr. Alaa El Hadad, Professor of Pediatric Oncology, National Cancer Institute and Prof. Dr. Lobna Mohamed Shalabe, Professor of Pediatric Oncology, National Cancer, Institute.

I would like also, to thank all patients who shared in this work for their cooperation.

Shaimaa Hassan Ramadan

List of Contents

Title	Page No.
List of Tables	i
List of Figures	iv
List of Abbreviations	v
Introduction and Aim of the Work	**1**
Review of Literature:	**3**
○ Primary Humoral Immunodeficiency Disorders	3
○ Lymphoid Malignancies	21
○ Lymphoproliferative Disorders Related To Primary Immunodeficiency Diseases	40
Subjects and Methods	**51**
Results	**60**
Discussion and Conclusion	**82**
Summary	**91**
Recommendations	**94**
References	**95**
Arabic Summary	**_**

LIST OF TABLES

No	Title	Page
1	Classification of primary immunodeficiency disorders: A)Predominantly antibody deficiencies B)Combined T-cell and B-cell immunodeficiencies C)Other well defined immunodeficiency syndromes D) Diseases of immune dysregulaton	8-13
2	Warning Signs of Primary Immunodeficiency Disorders	15
3	Pattern of infection in the more common Primary Immunodeficiency Disorders	16
4	Laboratory Tests in Immunodeficiency	19
5	Reference ranges of serum immunoglobulin levels in relation to age	20
6	WHO classification of the mature B-cell, T-cell, and NK-cell neoplasms	21-22
7	Ann Arbor staging system for Hodgkins lymphoma, including the Cotswolds modifications	31
8	St Jude staging system for Childhood non Hodgkin's lymphoma	31
9	Histologic classification of Hodgkin's lymphoma	32
10	Histologic classification of high grade non Hodgkin's lymphoma	33
11	FAB classification of Acute Lymphoblastic Leukemia	34
12	Histologic ,Immunophenotypic , Molecular and Cytogenetic Analysis of Different types of lymphomas encountered in children	35

LIST OF TABLES (Cont.)

No	Title	Page
13	Common Non random Chromosomal trans-locations in Childhood ALL	36
14	Imaging Evaluation of Children with Lymphoma	37
15	Prognostic factors of patient risk for failure to current treatment regimen	38
16	Distribution of neoplasias associated with different immunodeficiency states	40
17	Risk of malignancies in immunodeficiency disorders	41
18	Lymphoproliferative disorders in selected immunodeficiency states	44
19	Immunodeficiency disease related (IDR) scores	55
20	Age distribution of the three studied types of malignancy	60
21	Sex distribution of the three studied types of malignancy	62
22	Distribution of the weight/age and height /age percentiles among the three studied types of malignancy	62
23	Distribution of the clinical presentations in the studied sample	63
24	Distribution of different criteria of IDR score among the three studied types of malignancy	64-65
25	Comparison of IDR score at 2 different levels (6 and 8) in the three studied types of malignancy	67
26	Distribution of IDR score <6 among population under study	67

LIST OF TABLES (Cont.)

No	Title	Page
27	Comparison between lymphocytes levels and immunoglobulin levels as regard the distribution of IDR score	69
28	Comparison between weight/age and height/age percentiles as regard the distribution of IDR	70
29	Comparison between the three studied types of malignancy as regard neutrophils absolute count, lymphocytes absolute count, and serum LDH	70
30	Comparison between the three studied types of malignancy according to IgM Level	71
31	Comparison between the three studied types of malignancy according to IgA Level	72
32	Comparison between the three studied types of malignancy according to IgG Level	73
33	Correlation between age and Immunoglobulin	74
34	Distribution of IDR score among living and dead patients	74
35	Distribution of different variables among living and dead patients	75
36	Demographic and laboratory criteria of patients with IDR ≥8	77
37	Demographic and laboratory criteria of patients with complications of vaccination	78
38	Demographic and laboratory criteria of patients with previous sibling death	78
39	Demographic and laboratory criteria of patients with weight/age <3rd percentile	80
40	Demographic and laboratory criteria of patients with Lymphopenia	81

LIST OF FIGURES

No	Title	Page
1	Age distribution of the three studied types of malignancy	61
2	Distribution of IDR score <6 among population under study	68
3	Relation between the IDR scores (≥ 8 and <8)and serum IgM levels	69
4	Distribution of IgM levels among the three studied types of malignancy	71
5	Distribution of IgG levels among the three studied types of malignancy	73
6	Distribution of lymphocyte absolute count among living and dead patients	75
7	Distribution of IgG absolute count among living and dead patients	76

LIST OF ABBREVIATION

Abbreviation	Meaning
AD	Autosomal-dominant inheritance
ADA	Adenosine deaminase
ALCL	Anaplastic large cell lymphoma
ALL	Acute Iymphoblastic leukemia
ALPS	Autoimmune lymphoproliferative syndrome
AR	Autosomal-recessive inheritance
AT	Ataxia Telangectasia
ATM	Ataxia Telangectasia mutated
BL	Burkitt's lymphomas
BLL	Burkitt's-like lymphoma
BLNK	B-cell linker protein
BM	Bone marrow
BTK	Bruton agammaglobulinemia tyrosine kinase
CBC	Complete blood count
CD	Cluster of differentiation
CNS	Central nervous system
CTL	Cytotoxic T lymphocytes
CVID	Common variable immunodeficiency
DCLRE	DNA cross-link repair protein 1C
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EFS	Event free survival

LIST OF ABBREVIATION (Cont.)

Abbreviation	Meaning
FAB	French American British
FIM	Fulminant infectious mononucleosis
FISH	Fluorescent in situ hybridization
G6PDH	Glucose-6-phosphate dehydrogenase
HIES	Hyper-IgE syndrome
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HLA	Human leukocyte antigen
HRS	Hodgkin-Reedsternberg
IDR	Immunodeficiency disease related
IgA	Immunoglobulin A
IGAD	Immunoglobulin A deficiency
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IPEX	Immunedysregulation, polyendocrinopathy, enteropathy, X-linked
JAK3	Janus kinase 3
KS	Kaposi's sarcoma
LAD	Leucocyte adhesion defect
LBCL	Large B-cell lymphoma
LPD	Lymphoproliferative disease

LIST OF ABBREVIATION (Cont.)

Abbreviation	Meaning
MALT	Mucosa-associated lymphoid tissue
MRD	Minimal residual disease
MRI	Magnetic resonance image
NHL	Non Hodgkin's lymphoma
NK	Natural killer
PB	Peripheral blood
PB-LBL	Precursor B-cell lymphoblastic lymphoma
PCR	Polymerase chain reaction
PID	Primary immunodeficiency
PMLBL	Primary mediatinal (thymic) large B cell lymphoma
PNP	Purine nucleoside phosphorylase
RAG	Recombinase activating gene
RMRP	RNA of mitochondrial RNA-processing endoribo-nuclease
SCID	Severe combined immunodeficiency
SSCP	Single-strand conformation polymorphism
TCR	T-cell receptor
T-LBL	Precursor-T-cell lymphoblastic lymphoma
UNG	Uracil-DNA glycosylase
WAS	Wiskott-Aldrich syndrome
WBC	White blood cell
XL	X-linked inheritance

INTRODUCTION AND AIM OF THE WORK

Primary immune deficiency (PID) diseases represent a class of disorders in which there is an intrinsic defect in the human immune systems. More than 150 primary immunodeficiency syndromes have been described to date ***(Chinen et al., 2007).***

Lymphoid malignancies are a heterogenous group of disordres that occurs a result of neoplastic transformation of B and T cell development. The lymphoid malignancies can be broadly categorized into malignant lymphomas, which include non Hodgkin's lymphoma and Hodgkin's lymphoma, and acute and chronic lymphoid leukemias ***(Rezuke et al., 1997)***.

In primary immunodeficiencies, the true incidence of lymphoproliferative diseases is difficult to evaluate and has been estimated to be between 1.4% and 24% depending on the type of primary immunodeficiency. Their histological spectrum ranges from non-specific reactive hyperplasia to atypical lymphoid hyperplasia and lymphoma. However, the real nature of LPDs in primary immunodeficiencies is difficult to ascertain since only a few of them have been studied using immunohistochemistry, molecular biology or cytogenetic techniques ***(Canioni et al., 2001).***

Among 727 patients registered to the Japan immunodeficiency registery 25 patients were reported to have developed malignant neoplasms. The incidence of malignant

neoplasms in these patients was 3.2% ***(Kobayashi, 1987).*** In another study Kobayashi and Collegues, reported that the occurrence of malignant neoplasms among registered cases of primary immunodeficiency syndrome was 200-300 times that in the general population ***(Kobayashi, 1985).***

This study was aimed to evaluate the humoral immune status of children with lymphoid malignancies (Hodgkin's lymphoma, non Hodgkin's lymphoma, and acute lymphoblastic leukemia) in order to consider the possibility of primary immunodeficiency as a risk factor of malignancy.

PRIMARY HUMORAL IMMUNODEFICIENCY DISORDERS

Introduction:

The human body has an elaborate system of local and systemic, immune (cellular, humoral) and nonimmune (skin, mucous membranes) defense mechanisms to protect itself against microbal invaders. Disorders of this intricate system of host defense may generally be classified as primary or secondary ***(Bernatowska, 2001).***

The immune system is divided into two major components: innate and adaptive immunity. The adaptive immune system is slower to react and is the second line of defense. It has two arms: cellular and humoral. The cellular immune response is mediated primarily by T cells ***(Cooper et al., 2003).***

T lymphocytes mature in the thymus and are classified into subsets by markers on their outer surfaces and function. Most mature into CD4+ or CD8+ cells, while a smaller percentage become NK cells ***(Atkinson et al., 2000).***

The humoral arm depends on B cells, lymphocytes that mature in the bone marrow and reside in lymphoid organs ***(Sompayrac, 2003).*** When a mature B cell is stimulated by antigen, it becomes activated and undergoes clonal expansion. During this clonal expansion, progeny of the parent B cell undergo a series of immunoglobulin heavy-chain gene

rearrangements that result in the juxtaposition of the variable-region DNA sequences with different heavy-chain constant-region genes. A final step of B-cell differentiation involves terminal differentiation of B cells into immunoglobulin-producing plasma cells ***(Sneller et al., 1993).***

Antibodies are classified by their structure into one of five classes: IgG, IgA, IgM, IgD and IgE (presented in decreasing order of abundance). Most antibodies found in serum are IgG isotypes, with lesser amounts of IgA, IgM and IgE. Secretions such as saliva contain primarily IgA and IgM classes of antibodies. These antibody isotypes come from different plasma cell populations, even though they all bind the same antigen ***(Atkinson et al., 2000).***

Immunocompromised refers to an immune system in which the ability to resist or fight infections and tumors is subnormal, in other words, a condition in which the immune system is not functioning normally ***(Neil, 2007).***

Primary immune deficiencies are categorized according to the division of labor within the immune system by grouping the disorders based on the primary cellular target of the defect. Immune deficiencies involving the adaptive immune system are separated further into those primarily affecting T lymphocyte (cellular) immune function and those primarily affecting B lymphocyte (humoral) immune function ***(Thomas, 2006).***

Primary T cell disorders are rare, accounting for approximately 11% of reported primary immunodeficiencies, and generally present in infancy or early childhood ***(Edgar,***

2008). Meanwhile primary antibody deficiencies though relatively rare yet, account for the majority of primary immunodeficiency syndromes encountered in clinical practice ***(Herriot and Sewell, 2008).***

Incidence:

Primary immunodeficiencies generally are considered to be relatively uncommon. There may be as many as 500,000 cases in the United States, of which about 50,000 cases are diagnosed each year ***(Cooper et al., 2003).***

IgA deficiency is a common immunologic abnormality, affecting approximately 1 in 300 to 700 individuals ***(Ballow, 2002).***The prevalence of IGAD may be higher in male patients and may even have a seasonal pattern, with highest levels occurring in winter. CVID affects approximately 1 in 50,000 to 1 in 75,000 individuals ***(Bonilla et al., 2005).*** Hyper-IgM syndromes frequency is 1 in 100,000 births ***(Péron et al., 2007).*** X-linked SCID (XSCID) has an incidence of 1 of 50,000 to 100,000 live births ***(Bonilla et al., 2005).***

To study the frequency of primary immunodeficiencies in various regions of the Latin American continent, eight countries have collected information of 1428 patients ***(Zelazko et al., 1998).*** Predominantly antibody deficiencies were reported in 58% of patients, followed by cellular and antibody immunodeficiencies associated with other abnormalities in 18%, immunodeficiency syndromes associated with granulocyte dysfunction in 8%, phagocytic disorders in 9%, combined cellular and antibody immunodeficiencies in 5%, and complement deficiencies in 2% of patients ***(Zelazko et al., 1998).***