INTRODUCTION

The primary immune deficiencies constitute a heterogeneous group of disorders with a variable degree of deficiency in B cell and/ or T cell function. Malignancy is the second most common cause of death in pediatric age, and NHL is the third most common cancer affecting children. The NHL subtypes that occur are usually of high grade pathology, diffuse and often extranodal, and EBV is commonly identified in NHL, B- cell type. Burkitt lymphoma occurs mainly in x-linked lymphoproliferation, and T-cell tumors commonly occur in patients known to have ataxia-telangiectasia. The relative risk of NHL associated with these conditions varies from 30 to 200 ***(Filipovich et al., 1992).***

In ***2006, Yarmohammadi et al.,*** proposed a clinical scoring system for identifying children at risk of primary immune deficiency disorders. Similarly the Center of Disease Control (CDC) suggested 10 warning clinical signs of primary immune deficiencies.

Whether or not subtle, subclinical, immune deficiency is a risk factor for NHL is a key question in lymphoma research. This question can probably only be addressed by measuring genetic determinants of immune function or by measuring immune function years before NHL, development in longitudinal studies. Another approach that has been recently

used in studies of Hodgkin lymphoma is to examine immune phenotypes in identical twins of patients ***(Cozen et al., 2004)***.

Kersey et al., (1988) studied in August, 1986, 514 cases of naturally occurring immunodeficiencies registered at the Immunodeficiency Cancer Registry. Overall non-Hodgkin's lymphomas predominated in these patients, accounting for 48.6% of all cases. Non-Hodgkin's lymphoma was the predominant malignancy in ataxia-telangiectasia, common variable immunodeficiency, Wiskott-Aldrich syndrome (WAS) and severe combined immunodeficiency (SCID). The histopathology of the lymphomas differed somewhat in each of the disorders. In WAS, large cell "histiocytic" lymphoma predominates, with most cases having the features of B lymphocytes, including pleomorphic immunocytoma and immunoblastic lymphoma. Non-Hodgkin's lymphoma in SCID also generally had B cell features. The lymphomas in ataxia-telangiectasia are very heterogeneous with representation from all the major histologic subtypes

AIM OF THE WORK

To examine newly diagnosed pediatric lymphoma patients for possible associated primary cellular immune deficiency disorders by suggestive history and clinical scoring for PID as well as by studying the laboratory profile of cell mediated immunity

Chapter I
LYMPHOID NEOPLASMS

Introduction:

Lymphoid neoplasms, including lymphoma and lymphoid leukemia, arise from the malignant transformation of normal lymphoid cells at various stages of differentiation ***(Morton et al., 2007).***

Although some lymphoid neoplasms have been linked to certain infections and severe immunosuppression, the etiologies of most lymphoid neoplasms remain largely unknown, and evidence from descriptive and analytical epidemiologic studies increasingly points to etiologic heterogeneity among the lymphoid neoplasm subtypes ***(Rothman et al., 2006)***.

Lymphoma classification in the third millennium:

The WHO classification has been updated in the past 2 years, Published in September 2008, it builds upon the advances of the past and makes some in roads into better defining heterogeneous or ambiguous categories of disease. Some changes include the introduction of provisional borderline categories, the recognition of small clonal lymphoid populations, and the identification of diseases characterized by involvement of specific anatomic sites or by other clinical features such as age ***(Jaffe et al., 2008).***

Table (1): WHO classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008):

Mature B-cell neoplasms	
Chronic lymphocytic leukemia/small lymphocytic lymphoma	B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma	Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable	Hairy cell leukemia-variant
Splenic diffuse red pulp small B-cell lymphoma	
Lymphoplasmacytic lymphoma	Waldenström macroglobulinemia
Heavy chain diseases	Alpha heavy chain disease
Gamma heavy chain disease	Mu heavy chain disease
Plasma cell myeloma	Solitary plasmacytoma of bone
Extraosseous plasmacytoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	
Nodal marginal zone lymphoma	Pediatric nodal marginal zone lymphoma
Follicular lymphoma	Pediatric follicular lymphoma
Primary cutaneous follicle center lymphoma	Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS	T-cell/histiocyte rich large B-cell lymphoma
Primary DLBCL of the CNS	Primary cutaneous DLBCL, leg type
EBV_ DLBCL of the elderly	DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis	Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma	ALK_ large B-cell lymphoma
Plasmablastic lymphoma	
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease	
Primary effusion lymphoma	
Burkitt lymphoma	
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma	
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma	
Mature T-cell and NK-cell neoplasms	
T-cell prolymphocytic leukemia	T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells	Aggressive NK cell leukemia
Systemic EBV_ T-cell lymphoproliferative disease of childhood	Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma	Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma	Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma	Mycosis fungoides
Sézary syndrome	Lymphomatoid papulosis
Primary cutaneous CD30_ T-cell lymphoproliferative disorders	
Primary cutaneous anaplastic large cell lymphoma	
Primary cutaneous gamma-delta T-cell lymphoma	
Primary cutaneous CD8_ aggressive epidermotropic cytotoxic T-cell lymphoma	
Primary cutaneous CD4_ small/medium T-cell lymphoma	
Peripheral T-cell lymphoma, NOS	
Angioimmunoblastic T-cell lymphoma	
Anaplastic large cell lymphoma, *ALK*	
Hodgkin lymphoma	
Nodular lymphocyte-predominant Hodgkin lymphoma	Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma	Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma	
Lymphocyte-depleted classical Hodgkin lymphoma	
Posttransplantation lymphoproliferative disorders (PTLD)	
Early lesions	
Plasmacytic hyperplasia	
Infectious mononucleosis-like PTLD	
Polymorphic PTLD	
Monomorphic PTLD (B- and T/NK-cell types) †	
Classical Hodgkin lymphoma type PTLD†	

†These lesions are classified according to the leukemia or lymphoma to which they correspond ***(JAFFE et al., 2008).***

CHILDHOOD LYMPHOMAS

Nature of Lymphoma in Children:

Lymphomas arise from the constituent cells of the immune system or from their precursors and are the consequence of genetic aberrations that impair proliferation, differentiation, and ability to undergo apoptosis of lymphatic cells. Hodgkin disease (HD) and non-Hodgkin lymphomas (NHL) constitute 10%–15% of all childhood cancers in developed countries and are third in frequency after acute leukemias and brain tumors. All organ systems may be involved at some stage of the disease, including the central nervous system, head and neck, thorax, abdomen, gonads, and bone. However, at onset, nodal and splenic involvements are more common in Hodgkin disease, whereas extranodal involvement is more frequent in non-Hodgkin lymphomas ***(Toma et al., 2007).***

Structure of the lymphoid system:

Cellular composition of the lymphoid tissues

Lymphoid tissue, together with recirculating lymphocytes, constitutes the lymphoid system, which serves as one of the defense mechanisms of the organism against bacteria, viruses, parasites and toxins. The following cells, which are all involved in the defense and/or in the regulation of immune response, can be identified in lymphoid tissue:

- B cells
- T cells
- Natural killer (NK) cells
- Macrophages
- Follicular dendritic cells (FDC)
- Interdigitating dendritic cells (IDC)
- High endothelial venules (HEV)

(Rolink et al., 2001)

I. Non-Hodgkin lymphoma

Non-Hodgkin lymphomas (NHL) comprise approximately 10% of all childhood cancers and are a diverse collection of malignant neoplasms of lymphoreticular cells. Pediatric NHL includes a varied group of neoplasms that derive from both mature and immature (blastic) cells of both B-cell and T-cell origin. These neoplasms in children are typically intermediate to high grade (clinically aggressive) tumors. This is indirect contrast to NHL in adults, in which more than two-thirds of the tumors are indolent, low-grade malignancies ***(Perkins et al., 2000).***

Pediatric NHL also appears very different from adult lymphomas in that all of the tumors are diffuse neoplasms, and follicular (nodular) lymphomas are exceedingly rare. Similarly, the immunophenotypic subclassification of pediatric NHL shows marked differences from adult lymphomas. Pediatric NHLs are almost evenly split between B- and T-cell neoplasms, whereas T-

cell neoplasms make up less than 10% of adult NHL. Pediatric NHL also has many more lesions that are derived from blast-like or precursor B or T cells than are seen in adults ***(Swerdlow et al., 2004).***

Table (2): Correlation of histopathology, immunophenotype, clinical features, cytogenetics, and molecular features in childhood non-hodgkin lymphoma:

Histology	Immunology	Clinical Features	Cytogenetics	Genes Involved
Burkitt and Burkitt-like	B cell (sIg+)	Abdominal masses, gastrointestinal tract tumors, involvement of Waldeyer's ring	t(8;14)(q24;q32)	IgH-c*MYC*
			t(2;8)(p11;q24)	Ig‹-c*MYC*
			t(8;22)(q24;q11)	Ig»-c*MYC*
Diffuse large B-cell	B cells of germinal center or post germinal center	Abdominal masses, gastrointestinal tract tumors, involvement of Waldeyer's ring	t(8;14)(q24;q32)	IgH-c*MYC*
			t(2;17)(p23;q23)	*CLTC-ALK*
Mediastinal large B-cell	B cells of medullary thymus	Mediastinum		
Anaplastic large cell	T cell (mostly), null cell or NK cell ($CD30^+$)	Skin, nodes, bone	t(2;5)(p23;q35)	*NPM-ALK*
			t(1;2)(q21;p23)	*TPM3-ALK*
			t(2;3)(p23;q21)	*TFG-ALK*
			t(2;17)(p23;q23)	*CLTC-ALK*
			t(X;2)(q11-12;p23)	*MSN-ALK*
			inv 2(p23;q35)	*ATIC-ALK*
Precursor T lymphoblastic	T cell (thymocyte phenotype)	Anterior mediastinal mass with upper torso adenopathy	t(1;14)(p32;q11)	TCR ´-*TAL1*
			t(11;14)(p13;q11)	TCR´-*RHOMB2*
			t(11;14)(p15;q11)	TCR ´-*RHOMB1*
			t(10;14)(q24;q11)	TCR ´-*HOX11*
			t(7;19)(q35;p13)	TCR-*LYL1*
			t(8;14)(q24;q11)	TCR ´-*MYC*
			t(1;7)(p34;q34)	TCR-*LCK*
Precursor B lymphoblastic	B-cell precursors	Cutaneous masses and isolated lymph node masses		

NK, natural killer.

(Micheal et al., 2006)

Subtypes and Staging

There are four major pathologic subtypes of pediatric NHL that will be discussed in further detail below: Burkitt lymphomas (BL), diffuse large B-cell lymphoma (DLBCL),

anaplastic large cell lymphoma (ALCL) and lymphoblastic lymphomas (LBL) ***(Perkins et al., 1995)***.

Table (3): The St Jude staging system for childhood non-Hodgkin lymphoma:

Stage I

A single tumor (extranodal) or single anatomic area (nodal), excluding mediastinum or abdomen.

Stage II

A single tumor (extranodal) with regional node involvement on same side of diaphragm:

a) Two or more nodal areas
b) Two single (extranodal) tumors with or without regional node involvement

A primary gastrointestinal tract tumor (usually ileocecal) with or without associated mesenteric node involvement, grossly completely resected

Stage III

On both sides of the diaphragm:

a) Two single tumors (extranodal)
b) Two or more nodal areas

All primary intrathoracic tumors (mediastinal, pleural, thymic)

All extensive primary intra-abdominal disease; unresectable

All primary paraspinal or epidural tumors regardless of other sites

Stage IV

Any of the above with initial CNS or bone marrow involvement (<25%)

(Armitage et al., 2005)

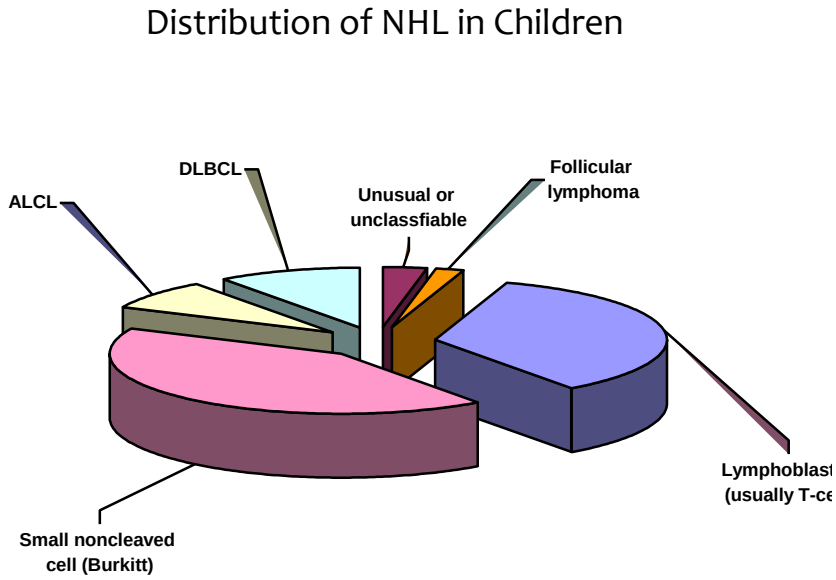

Figure (1): Schematic representation demonstrating the pediatric NHL (highlighting the higher incidence of more aggressive lymphomas in children) ***(Sandlund et al., 1996)***

1. Burkitt Lymphomas:

Incidence:

Burkitt's lymphoma accounts for 40−50% of pediatric NHL in nonendemic areas. Cases occurring outside of Africa are morphologically indistinguishable from those occurring in the endemic areas. However, endemic BL tends to have a high propensity for involvement of the bones of the face (particularly the jaw and maxilla) and occurs in younger children. The non endemic or sporadic form of BL also tends to involve extranodal sites, but is more common in the GI tract, particularly the ileocecal area, as well as in the kidneys and ovaries; by contrast,

involvement of the bones of the face is unusual ***(Diebold et al., 1999)***.

A small percentage, 1−2% of patients, may present with disseminated disease including extensive peripheral blood and bone marrow involvement ***(Cairo et al., 2003).***

2. Diffuse Large B-cell Lymphoma

Incidence:

Diffuse large B-cell lymphomas (DLBCL) make up approximately 20% of pediatric NHL. DLBCL tends to occur in slightly older age groups and is the most common histology of NHL seen in children older than 5 years of age and teenagers. DLBCL frequently occurs at a single site, with mediastinal and abdominal disease being most common. Nodal disease is also common; in contrast to BL. Diffuse large B-cell histology is also strongly associated with immunodeficiency states (inherited or iatrogenic) and is the most common subtype of immunodeficiency-associated lymphoma seen in childhood ***(Cairo et al., 2003).***

3. Anaplastic Large-Cell Lymphoma

Incidence:

Anaplastic large-cell lymphoma (ALCL) is the most common mature T-cell lymphoma seen in children and makes up approximately 10% -15% of all pediatric non-Hodgkin lymphoma (NHL) and approximately 30−40% of the large-cell lymphomas seen in the pediatric population ***(Burkhardt et al., 2005).***

4. Lymphoblastic Lymphoma:

Incidence:

The malignant lymphomas are the third most common malignancy in childhood, among children less than 15 years of age, there is a slight predominance of non-Hodgkin lymphoma over Hodgkin lymphoma ***(Percy et al., 1999).***

The most commonly encountered histologic subtypes of non-Hodgkin lymphoma in children according to the WHO classification include Burkitt lymphoma, diffuse large B-cell lymphoma, anaplastic large-cell lymphoma, and precursor B and precursor T lymphoblastic lymphoma. Among these, the lymphoblastic lymphomas account for approximately 30% of childhood NHL ***(Sandlund et al., 1996).***

Table (4): Work up for staging of B-cell lymphomas

1- Physical examination.

2- Complete blood count.

3-Laboratory tests: Serum electrolytes

Liver and renal serum tests

Serum LDH-Serum uric acid

4-Imaging studies:

a- Chest X-ray, Chest CT scan (if chest X-ray film abnormal or suspiciously abnormal), Thoracic ultrasound (e. g., for following thoracic tumor).

b- Abdominal ultrasound examination (include liver/spleen, kidneys, abdomen, pelvis). Abdominal CT scan

c- Gallium67 scan

d- MRI of head and neck region/brain

e- Whole body MRI

f- FDP-glucose PET

5-Bone marrow examination

6- CSF examination (cytology)

Useful or sometimes indicated investigations

- Serum lactate (especially in the presence of a large tumor)
- Bone scan (for more precise documentation of bony lesions)
- Endoscopy (e. g. for GI bleeding)
- CSF=cerebrospinal fluid; LDH=lactate dehydrogenase

(Magrath et al., 2007)

II. Hodgkin Lymphoma

Introduction:

The recommended term "Hodgkin lymphoma (HL)" encompasses two basic diseases, a relatively common form now referred to as classical Hodgkin lymphoma (CHL) and the very uncommon disease of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), Classical HL is a malignant tumor that may be subclassified into histological groups sharing biologically and morphologically similar neoplastic cells, Hodgkin Reed-Sternberg (HRS) cells. NLPHL is in contrast viewed as an indolent tumor sharing features with some B-cell non-Hodgkin lymphomas ***(Stein et al., 2001a).***

Epidemiologic Features:

HD has a bimodal age distribution: In developed countries the first peak occurs in the middle to late 20s and the second peak after the age of 50 years, whereas in developing countries the early peak occurs before adolescence. HD is very rare in children younger than 5 years. The prevalence in males and females is roughly the same ***(Toma et al., 2007).***

The childhood form of Hodgkin lymphoma tends to increase with increasing family size and decreasing socioeconomic status. In contrast, the young adult form of Hodgkin lymphoma is associated with a higher socioeconomic status in industrialized countries ***(Chang et al., 2004).***

Association with EBV:

Epstein-Barr Virus (EBV) has been widely implicated as a possible etiologic agent in CHL. Epidemiological studies indicate that EBV is mostly associated with mixed cellularity type HL, shows a male predominance, is more frequent among children under the age of 10 and older patients, compared to young adults, and is also more frequent with lower education level or socioeconomic status ***(Gandhi et al., 2004).***

Table (5): Histologic classification of hodgkin lymphoma according to the who classification

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis subtype
Mixed cellularity subtype
Lymphocyte-rich subtype
Lymphocyte depleted subtype

(Stein et al., 2001)