

# Childhood lymphomas in Yemen

## Clinicopathological study

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### ABSTRACT

**الأهداف:** معرفة مدى تكرار حدوث الليمفوم في أطفال اليمن لجميع الأعمار ومعرفة أنماطه وعلاقته بالجنس ومكان الإصابة.

**الطريقة:** أجريت دراسة وصفية تعتمد على سجلات 1167 مصاب بليمفوم تم تشخيصهم لدى ثلاثة استشاريين في قسم علم الأمراض كلية الطب والعلوم الصحية- جامعة صنعاء- اليمن، خلال الفترة من 1 يناير 2004 إلى 30 ديسمبر 2007. وتم التشخيص المجهرى لعينات الأنسجة المصبوغة بصبغة الهيماتوكسلين والايوسين، وقد تم تصنيف حالات لمفوم لاهودجن (NHL) طبقاً لتصنيف المعهد الوطني للسرطان والمتبع عالمياً في تصنيف أورام ليمفوم لاهودجن في الأطفال وتم تصنيف مرض هودجن (HD) طبقاً لتصنيف راي المتبع عالمياً.

**النتائج:** من بين 1167 حالة ليمفوم هناك 801 (68.6%) حالة لاهودجن (NHL) و 366 (31.4%) حالة هودجن (HD) وكانت هناك 347 (29.7%) حال من بين هذه الحالات في الأطفال الذين تتراوح أعمارهم 18 سنة وأقل، وقد توزعت هذه الحالات بين ليمفوم لاهودجن 221 (63.7%) ومرضى هودجن 126 (36.3%). أوضحت النتائج مدى تكرار الليمفوم الخبيث على النحو التالي: ليمفوم باركت 64.8%، ليمفوم الخلايا الكبيرة المنتشرة 23%، ليمفوم الأورمة الليمفاوية 6.3%، وشكلت بقية الأنماط الأخرى النسبة 5.9%. وأما بالنسبة لمرض هودجن فقد شكل مزوج الخلية نسبة 72.3%، بلغت نسبة سيادة اللمفاويات حوالي 16.6% والتصلب العقدي 7.9% ونفاد اللمفاويات 0.8% وحالات غير مصنفة 2.4%. تتراوح نسبة الإناث للذكور 1:1.7. تبلغ نسبة الأنسجة العقدية 205 59% حالة و 142 41% حالة غير عقدية. كما أوضحت الدراسة أن جميع حالات هودجن عقديه بينما شكلت حالات لاهودجن 62.6% لا عقدية و 37.4% عقدية.

**خاتمة:** تبين الدراسة أن الليمفوم في الأطفال يظهر بدرجة خطرة وذلك في مرض لاهودجن وبنوع أقل خطورة لدى هودجن. تشير الدراسات إلى تماثل إصابات الليمفوم لدى الأطفال اليمنيين مع ما تظهره الدراسات العالمية المتنوعة.

**Objectives:** To find out the frequency of childhood lymphomas in all ages, and to describe patterns of lymphomas in relation to gender and site in Yemen.

**Methods:** This is a descriptive record-based study of 1167 cases of lymphomas diagnosed by 3 pathologists in the Department of Pathology, Sana'a University, Sana'a, Yemen from 1st January 2004 to 30th December 2007. The diagnoses were made on hematoxylin and eosin stained, and categorized non-Hodgkin's lymphoma (NHL) according to the National Cancer Institute Working Formulation classification, and Hodgkin's disease (HD) according to Rye classification.

**Results:** Out of 1167 lymphomas, 801 (68.6%) were NHL, and 366 (31.4%) were HD, amongst these 347 (29.7%) were patients aged  $\leq 18$  years, and 221 (63.7%) had NHL, and 126 (36.3%) had HD. The NHL found was Burkitt (64.8%), diffuse large cell lymphoma (23%), lymphoblastic lymphoma (6.3%), and other miscellaneous types account for 5.9%. The histological types of HD were mixed cellularity (72.3%), lymphocyte predominance (16.6%), nodular sclerosis (7.9%), lymphocyte depletion (0.8%), and nonclassified cases (2.4%). The female to male ratio was 1:1.7. The nodal site accounts for 205 (59%) cases, and 142 (41%) were extranodal. The HD was totally nodal, whereas NHL showed 37.4% nodal, and 62.6% extranodal.

**Conclusion:** Childhood lymphomas in this study is of high grade NHL, and of less favorable prognostic type in HD. This indicates that childhood lymphomas in Yemen have similar patterns as that found in other international studies.

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Lymphoma is the primary malignant neoplasm of lymphoid tissue, and is considered as the third most common cancer in children worldwide. The 2 broad categories of lymphomas, non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) have different clinical manifestations, microscopic morphology, treatment, and prognosis.<sup>1</sup> The NHLs comprises a heterogeneous group of tumors with distinct pathologic and clinical characteristics.<sup>2</sup> However, NHL is a relatively common cancer in children, and is the third most common cause of cancer death in this age group.<sup>3</sup> The NHL of children, in contrast to that of adults, is usually diffuse, extranodal, high grade,<sup>1,4</sup> and has different classification which bear a confusing array, and in childhood, these classifications bear little relationship to our understanding of the cell of origin, or pattern of behavior.<sup>5</sup> To lessen the confusion created by multiple classification schemes of NHL, the National Cancer Institute developed a histological system, known as the National Cancer Institute Working Formulation (NCIWF), which defines 3 primary subtypes of childhood NHL.<sup>5</sup> Hodgkin's disease has been traditionally used for a type of malignant lymphoma, in which Reed-Sternberg cells are present in a background of reactive inflammatory cells of various types, accompanied by fibrosis of variable degree.<sup>6</sup> The first report on HD in children was presented by Thomas Hodgkin in 1832, and in 1902 another 4 cases were described by Dorothy Reed. Since then, a number of studies have dealt with the histology, incidence, epidemiology, and prognosis of HD in childhood. It was reported that HD occurs more often in South American, Middle Eastern, and African children, than in North American and European children.<sup>1</sup> The aim of this study is to find out the frequency of childhood lymphomas among all ages, and to define the frequency and patterns of lymphomas in relation to gender and site in Yemeni children, and to compare the findings with other international studies.

**Methods.** A descriptive record-based study of 1167 cases of lymphomas was carried out in the Department of Pathology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen from 1st January 2004 to 30th December 2007. The diagnoses were made primarily in the private laboratories of 3 consultant pathologists in Sana'a, who received the histopathologic biopsies from Sana'a and other Yemeni provinces. The biopsies were fixed in 10% formalin solution before being processed by manual and automatic tissue processor (Shandon Southern product, Cheshire, England). After embedding in paraffin blocks, several thin sections of 2-3 micrometer thickness from each block were cut. The sections were stained with hematoxylin and eosin (H

and E) stain for routine histological diagnosis. During the histological analysis, the sample was evaluated on the type of tissue, total or partial effacement of architecture, nodular or diffused arrangement of cells, morphology of lymphocytes, mitotic activity, Reed-Sternberg cells, presence of inflammatory cells, and degree of fibrosis, and finally categorized NHL according to the NCIWF classification, and the HD according to Rye classification. The present study focuses on those cases that revealed clear histological picture of lymphoma on light microscope, and excludes the doubtful cases of suggestive lymphomas, or undifferentiated small round cell malignancy of most likely lymphomas. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine and Health Sciences of Sana'a University. The statistical analysis was carried out using the Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA) to calculate Chi square and *p*-value. A *p*-value of the frequency of childhood lymphoma among all ages was considered statistically significant.

**Results.** A total number of 1167 lymphomas were studied. The NHL was 801 (68.6%) and HD was 366 (31.4%). The patients aged  $\leq 18$  years were 347 (29.7%). The frequency of childhood lymphomas among all ages was found to be statistically significant ( $p=0.018$ ). In children, 221 (63.7%) had NHL, and 126 (36.3%) had HD (Table 1). Two hundred and eighteen were males and 129 were females. The female to male ratio was 1:1.7 with preponderance of boys. The highest histologic type of NHL was small non-cleaved Burkitt type (64.8%), followed by diffuse large cell lymphoma (23%), and lymphoblastic lymphoma (6.3%). The miscellaneous group constitutes 13 (5.9%), out of this 2 cases were of low grade small lymphocytic lymphoma and one was mixed small and large cell of intermediate grade. The remaining cases (4.5%) were diagnosed as NHL without specification (Table 2). The female to male ratio of NHL was 1:1.4. The youngest patient was a one-year-old boy. The youngest girl was 2 years old. The histological types of HD were mixed cellularity, lymphocyte predominance, nodular sclerosis, lymphocyte depletion,

**Table 1** - Distribution of adult and childhood lymphomas.\*

Type	Adult n (%)	Childhood n (%)	Total
Non-Hodgkin's lymphoma	580 (70.7)	221 (63.7)	801 (68.6)
Hodgkin's lymphoma	240 (29.3)	126 (36.3)	366 (31.4)
<b>Total</b>	<b>820 (100)</b>	<b>347 (100)</b>	<b>1167 (100)</b>

\*Chi square test - 5.6,  $p=0.018$

**Table 2 -** Gender distribution of childhood non-Hodgkin's lymphoma subtypes.\*

Type	Male n (%)	Female n (%)	Total
Burkitt	83 (65.4)	60 (63.8)	143 (64.8)
Lymphoblastic	9 (7.0)	5 (5.3)	14 (6.3)
<i>Diffuse large cell</i>			
High grade	12 (9.4)	8 (8.5)	20 (9.0)
Intermediate grade	6 (4.7)	5 (5.3)	11 (5.0)
Non-specified grade	12 (9.4)	8 (8.5)	20 (9.0)
<i>Miscellaneous</i>			
SLL+	1 (0.8)	1 (1.1)	2 (0.9)
MS & L++	-	1 (1.1)	1 (0.5)
Unspecified NH	3 (2.4)	7 (7.4)	10 (4.5)
<b>Total</b>	<b>127 (100)</b>	<b>94 (100)</b>	<b>221 (100)</b>

\*According to the National Cancer Institute Working Formulation classification,<sup>3</sup> SLL - small lymphocytic lymphoma of low grade, MS & L - mixed small and large cell lymphoma of intermediate grade

**Table 3 -** Gender distribution of childhood Hodgkin's disease subtypes.\*

Type	Male n (%)	Female n (%)	Total
Mixed cellularity	65 (71.4)	26 (74.3)	91 (72.3)
Lymphocyte predominance	16 (17.6)	5 (14.3)	21 (16.6)
Nodular sclerosis	8 (8.8)	2 (5.7)	10 (7.9)
Lymphocyte depletion	1 (1.1)	-	1 (0.8)
Nonclassifiable	1 (1.1)	2 (5.7)	3 (2.4)
<b>Total</b>	<b>91 (100)</b>	<b>35 (100)</b>	<b>126 (100)</b>

\*According to Rye classification<sup>16</sup>

**Table 4 -** Site distribution of lymphomas.

Site	HD n (%)	NHL n (%)
<i>Nodal</i>		
Cervical lymph nodes	104 (82.5)	37 (46.8)
Other sites	22 (17.5)	42 (53.2)
<i>Extranodal</i>		
Abdomen	-	101 (76.5)
Jaws	-	10 (7.6)
Other sites	-	21 (15.9)

HD - Hodgkin's disease, NHL - non-Hodgkin's lymphomas

and few non-classified cases. The female to male ratio in HD was 1:2.6 (Table 3). The youngest patient was a 3-year-old boy with mixed cellularity. The youngest girl was 5 years old. The nodal site accounts for 205 (59%) cases and 142 (41%) were extranodal. The HD presented totally as nodal, whereas, NHL shows 37.4%

nodal and 62.6% extranodal. The most common nodal site was cervical lymph nodes (46.8%) in NHL and 82.5% in HD. The extranodal site of NHL and other sites is shown in Table 4.

**Discussion.** Lymphomas comprise the third most common cancer in children worldwide with considerable variation.<sup>1,2</sup> In our present study, the frequency of childhood lymphomas among lymphomas of all ages was 29.7%. The NHL constituted 63.7%, and HD was 36.3%. These data is in agreement to that reported by Haddadin<sup>7</sup> from Jordan, and slightly differ from the findings noted in Nigeria by Obioha et al,<sup>8</sup> Akang,<sup>9</sup> and from Pakistan by Saleh et al.<sup>10</sup> The possible reasons for these variations are the criteria of diagnosis, number of cases, and geographical factors. The NHL in our study was therefore planned according to the NCIWF classification.<sup>5</sup> The most common histologic type in this study was Burkitt lymphoma, which constituted 64.8%, in contrast to the studies carried out in Thailand (84%)<sup>11</sup>, and Nigeria (92%).<sup>9</sup> Thomas et al<sup>12</sup> who studied lymphomas in Saudi Arabia noted that 95% of childhood NHL were Burkitt and lymphoblastic. But lower figures were observed in Jordan by Haddadin,<sup>7</sup> Almasri et al,<sup>13</sup> and in the United Kingdom by Wright et al.<sup>4</sup> Our findings were in general, intermediate between the previous findings. Diffuse large cell lymphoma was the second most frequent histologic type in this study, which was comparable to that showed by Almasri et al.<sup>13</sup> Wright et al's study<sup>4</sup> showed lower than this figure. Lymphoblastic lymphoma constituted 6.3% in our population, while much higher figures up to 24% were noted by other international studies.<sup>4,10</sup> A similar finding was reported in Nigeria by Ojesina et al.<sup>14</sup>

Our results showed more than 85% high grade type NHL, which were similar to that found by Wright et al,<sup>4</sup> Thomas et al,<sup>12</sup> and Perkins.<sup>15</sup> The HD in this study was conducted according to Rye classification.<sup>16</sup> The most common histologic type in this study was mixed cellularity (72.3%), in contrast to the studies carried out in the West,<sup>17</sup> where the mixed cellularity was less than 35%, but it is in agreement with some studies carried out in the Middle East countries.<sup>10,18,19</sup>

Childhood lymphocyte depletion appears very rare in the current study, and in that observed by Poppema and Lennert<sup>17</sup> in the United States. In general, it may be said that while comparing the frequency of histological types of childhood lymphomas in the present study and different international studies, a clear divergence was observed. Such divergence could be explained in terms of diagnostic approach and/or techniques applied, number of patients studied, as well as, culture, economical, racial, geographical, and immunological

differences. However, Epstein-Barr virus is mentioned as the prime candidate because of the association of some type of lymphomas, Burkitt and HD with a history of infectious mononucleosis, and the elevated antibodies to Epstein-Barr virus capsid antigens in serum from many patients with Burkitt and HD,<sup>20,21</sup> so this raised the possibility of a chronic stimulatory process of the lymphatic system in Burkitt and HD's, and may add another explanation for these variations. In the developing countries, patients usually consult very late, and the histological diagnosis is also delayed, so there is a possibility of transformation from one histological type of Hodgkin's lymphoma to another. Furthermore, untreated cases should be considered as noted by Poppema and Lennert.<sup>17</sup> It may be added that progression usually occurs toward a histologically more malignant form of HD, while the reverse is seldom possible. A distinct male predominance in all histologic types of NHL were seen in our study, similar to that reported by other authors.<sup>22,23</sup> In many previous international studies, a male preponderance was found in HD. In the present series 72.3% were male, and the female to male ratio was 1:2.6, which appears similar to the previous findings of some literature in all ages of HD.<sup>10,24</sup>

The extranodal site of NHL noted in this study was distributed in the abdomen, jaws, and other sites. The prominent extranodal sites in childhood NHL were reported in many literature.<sup>4,7,25</sup> The extranodal site in childhood NHL is different from that of adult NHL, where nodal represents 65% and extranodal 35%.<sup>16</sup> The most probable reason for the absence of extranodal site was the shortage of investigations, and clinical data. Our study was focused on morphological findings using the light microscope, and routine H and E stains. The immunohistochemistry technique, which is the most accurate technique is not available in Yemen, so we did not utilize the World Health Organization (WHO), and the Revised European-American Lymphoma Classification (REAL) technique.

In conclusion, childhood lymphomas in this study were almost of high grade in NHL, and of less favorable prognostic type mixed cellularity in HD. In NHLs, they fall mainly into these categories; Burkitt lymphoma, diffuse large cell lymphoma, lymphoblastic lymphoma with prominent extranodal site. In HD, it falls into mixed cellularity and totally of nodal site. These observations indicate that childhood lymphoma in Yemen has similar patterns, gender, and site distribution as that shown in other international studies. When the facilities for immunohistochemical technique becomes available, further studies are warranted using the modified REAL

and WHO classification to reduce the number of unclassified cases, and to identify the doubtful cases.

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#### Related topics

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