Research Article

B-cell Non-Hodgkin's lymphoma in children, demographic distribution and clinical presentation: An experience from the Child's Central Teaching Hospital in Baghdad, Iraq

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ABSTRACT

INTRODUCTION: Non-Hodgkin's lymphoma represents 6-8% of all malignancies in children. Mature B-cell Non-Hodgkin's lymphoma represents 60% of all Non-Hodgkin's lymphoma in children.

OBJECTIVE: To determine the demographic, clinical presentation, histopathological subtypes, and stages of patients admitted to the Child Central Teaching Hospital in Baghdad from 2010 to 2017 diagnosed with B-cell Non-Hodgkin's lymphoma in children.

METHODS: This descriptive retrospective study on 149 patients under 14 years admitted with B-cell Non-Hodgkin's lymphoma to the Child Central Teaching Hospital in Baghdad from 1 January 2010 to 31 December 2017.

RESULTS: We recorded 149 patients with B-cell Non-Hodgkin's lymphoma. Male to female ratio was 2:1, and eighty-nine patients (59.73 %) were below five years. The mean duration of illness before the presentation was six weeks. The abdomen was the most common primary site of involvement reported in 126 patients (84.56%). Burkitt lymphoma was the most common histopathological subtype in 83 patients (55.7%), followed by unclassified in 45 patients (30.2%) and diffuse large B-cell in 21 patients (14.09%). Most patients were in stages III and IV, 127 (85.23%).

CONCLUSION: B-cell Non-Hodgkin's lymphoma is more common in males below the age of five years. Burkitt lymphoma is the most common histopathological subtype and is usually presented in advanced stages.

Key words: B-cell, Non Hodgkin's lymphoma, Burkitt lymphoma, paediatric Iraq.

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a diverse collection of malignant neoplasms of lymphoid cell origin, including all the malignant lymphomas that are not classified as Hodgkin's disease (HL). NHL results from a malignant proliferation of cells of lymphocytic lineage. Although malignant lymphomas are generally restricted to lymphoid tissue such as lymph nodes, Peyer's patches, and the spleen, it was found in the bone marrow. Primary central nervous system and bone manifestations are rare.[1]

In patients under the age of 20 years, NHL represents approximately 6-8 % of all malignancies. In the US, for this age group, 750-800 new cases of NHL are reported annually, with an estimated incidence of 1 per 100,000. This incidence is gradually increased over the past 40 years. The incidence of NHL is geographically dependent; in equatorial Africa, Burkitt Lymphoma (BL) accounts for almost 50 % of all childhood cancers.[2]

Males are more commonly affected than females, with a ratio of 2-3:1. The median age of presentation is ten years, and it is uncommon to have NHL below the age of three years.[3]

Inherited or acquired risk factors are identified for NHL. Immunological defects like Bruton type of sex-linked agammaglobulinemia, com-

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mon variable agammaglobulinemia, Wisconsin Aldrich syndrome, and autoimmune lymphoproliferative syndrome; Post-transplant immunosuppressive; Lymphomatiod papulosis in children, Viruses like Epstein-Barr virus and human immune deficiency virus (HIV); and drugs and radiotherapy are examples of these risk factors.[3]

Pathologically, NHL is classified into four major subtypes. [3] Burkitt lymphoma (BL)(small noncleaved) constitutes about 40%, Lymphoblastic Lymphoma (LL) accounts for about 30%, diffuse large B cell lymphoma (DLBCL) accounts for about 20%, and anaplastic large cell lymphoma (ALCL) accounts for about 10%.

The clinical manifestations of childhood NHL depend primarily on pathological subtypes and sites of involvement. The rapidity of growth of the tumour and its size and location can cause more symptoms.[2]

The Child's Central Teaching Hospital (CCTH) is one of the major paediatric hospitals in Iraq, with a big haemato-oncology unit. Its catchment area included Baghdad and nearby provinces. Biostatistics of this centre is vital to draw a complete picture of the epidemiology of haematological malignancies in Iraq. So this study was designed to measure the demographic features, clinical presentations, histopathological subtypes, and staging of the patients with B cells NHL treated at the CCTH in Baghdad from 2010-2017.

METHODS

Setting and study design: A retrospective descriptive study was conducted in 2019 on patients' records at the Child's Central Teaching Hospital (CCTH) oncology unit in Baghdad from 1 January 2010 to 31 December 2017.

Ethical consideration: The ethical research committee of Al-Karkh Health Directorate has approved the proposal for this research. The administration of the CCTH agreed to use the records of patients for this study. The research was conducted according to the code of ethics of the Ministry of Health in Iraq.

Definition of the cases: Children aged 14 years and less with newly diagnosed B-cell NHL admitted to the haematology department at the Child's Central Teaching Hospital from 1 January 2010 to 31 December 2017. Histological diagnosis was based on the International Working Formulation (IWF) defined by National Cancer Institution (NCI).[4,5] Clinical staging was based on St. Jude Staging System.[2] Only four patients were excluded because of incomplete data records.

Procedure, data collection and outcomes: The following data were collected from the patient's records into a form designed by the authors, gender, age at the diagnosis, symptoms and signs at presentation, and the initial investigations, including complete blood count, liver and renal functions, serum electrolytes, and uric acid. For staging, parameters of the bone marrow aspiration/biopsy, cerebrospinal fluid examination, X-ray, sonography, CT scan and sometimes MRI were extracted.

For the sake of our study, haemoglobin was grouped into ≤ 10 and >10 gm/dl. Normal WBC count is 4-11 $x10^9$, normal platelet count was 150-450$x10^9$, normal serum creatinine 23-90 umol/l, and normal serum uric acid 120-420 mmol/dl.[3]

The diagnosis is based on histopathology through incisional/excisional biopsy or by FNAC. Immunohistochemical stains were unavailable, and serum lactate dehydrogenase (LDH) level was not performed for all cases because of the limited availability of tests.

Data analysis: Data are presented using Statistical package for social sciences version 24 (SPSS v24). Continuous variables are presented as means with standard deviation, and discrete variables are presented as numbers and percentages.

RESULTS

In this study, the total number of patients diagnosed with B-cell and admitted to the CCTH from 2010-2017 was 149, 18.6 per year. Males were more commonly affected than fe-

Table 1 | Demographic distribution, clinical presentation and diagnostic evaluation of B cell NHL

Variable	Category	N=149	100%
Gender	Male	102	68.45
	Female	47	31.54
Age Mean	5.4 years		
Groups	< 5 years	89	59.73
	5 - <10 years	41	27.51
	≥ 10 years	19	12.75
Duration of illness Mean	6 weeks		
Groups	>6 weeks	95	63.75
	≥ 6 weeks	54	36.24
Clinical presentation			
	Abdominal Distension	126	84.56
	Fever	107	71.81
	Pallor	74	49.66
	Peripheral LAP	30	20.13
	Hepatomegaly	24	16.10
	Splenomegaly	17	11.40
	Bleeding	6	4.02
The primary site of involvement*			
	Abdomen	126	84.56
	Peripheral Lymph node	30	20.13
	Thorax	4	2.68
	Jaw	4	2.68
	Others	3	2.01
Diagnostic Evaluation			
	Excisional/Incisional Biopsy	85	57.04
	FNA	58	38.92
	BMA	2	1.34
	Not recorded	4	2.68

* More than one primary site may occur in one patients. **LAP**: lymphadenopathy. **FNA**: Fine Needle Aspiration. **BMA**: Bone Marrow Aspiration

Table 2 | The haematological and biochemical laboratory investigations on presentation

Variable	Category	N	100 %
HB (g/dl)	≤10	102	68.45
	10>	47	31.54
WBC	High	53	35.57
	Normal	94	63.08
	Low	2	1.34
Platelets count	Normal	83	55.70
	High	61	40.93
	Low	5	3.35
Serum uric acid	Normal	118	79.19
	High	29	19.46
	Not recorded	2	1.34
Serum creatinine	Normal	84	56.37
	High	34	22.81
	Not recorded	31	20.80

males, 102 (68.45%) and 47 (31.54%), respectively, with a male-to-female ratio of 2.17:1. The commonest age group involved, was below the age of 5 years, 89 (55.9 %), followed by the age group 5-<10 years, 41 (27.51 %), and only 19 patients (12.75 %) were ten years and above. The duration of the symptoms on presentation ranged between 4 and 180 days; in 95 patients (63.75%) was less than six weeks and in 54 patients (36.24%) equal to or more than six weeks.

Abdominal distention was the most common presentation reported in 126 patients (84.56%), followed by fever in 107 (71.81%) patients, pallor in 74 (49.66%) and lymphadenopathy in 30 (20.13%). The most common primary site of involvement was the abdomen in 126 patients (84.56%), followed by the peripheral lymph node in 30 patients (20.13%). Most of the patients, 85 (57.04%), were diagnosed by excisional/incisional biopsy, and 58 patients (38.92 %) were diagnosed by FNA. For more details, see table 1.

The haematological data on the presentation of the patients were as follows: Hb level was more than 10 gm/dl in102(68.45%) patients with a range of 5 -15 gm/dl, a mean of 10± 3.3gm/dl, and a median of 10.5 gm/dl. The WBC count was high in 53 patients (35.57%) and normal in 94(63.08%) with a range of 2.28-28.60 $\times 10^9$/L, and a mean of 10.99±5.8 $\times 10^9$/L, and a median of 9.90 $\times 10^9$/L. The platelet count was normal in 83 patients (55.70%), low in 5(3.35%), and elevated in 61(40.93%), with a range of 42-1080/mm^3, and a mean of 283.7±275/mm^3, and a median of 366/mm^3.

Most patients, 118 (79.19%), have normal uric acid on presentation, while only 29 (19.46%) have high uric acid. On presentation, 84 patients out of 118 had normal serum creatinine, and 34 patients (22.8%) had a high level; in 31 patients (20.8%), serum creatinine was not recorded. For more details, see table 2.

Burkitt Lymphoma was the most common

Table 3 | Histopathological subtypes and staging of B-cell NHL.

Variables	N	100%
Histopathological subtype		
Burkitt Lymphoma	83	55.70
Unclassified*	45	30.20
DLBCL	21	14.09
Staging of B-cell NHL		
I	1	0.067
II	21	14.09
III	111	74.49
IV	16	10.73

DLBCL: Diffuse large B cell lymphoma

histopathological subtype reported in 83 patients (55.7%), followed by unclassified NHL in 45 patients (30.2%) and DLBCL in 21 patients (14.09%). Bone marrow examination was negative in 136 patients (91.27%) and positive in only 13 patients (8.72%). Also, CSF examination was negative in 145 patients (97.31%), positive in only three patients (2%), and not recorded in 1 patient (0.67%). Stage III was diagnosed in 111 patients (74.49%), stage II in 21 patients (14.09%), stage IV in 16 patients (10.73%) and stage I in only one patient (0.067%), see table 3.

DISCUSSION

We recorded 149 patients diagnosed with B-cell and admitted to the CCTH from 2010-2017, 18.6 per year. Male to female ratio was 2.17:1, which is the same ratio reported by Ibrahim in his study conducted at the CCTH in 2011,[6] Faizan M 2018 in Pakistan[7] and Salzburg J. in Germany 2007;[8] these studies found Male to Female ratios were 2:1,2.6:1,2.7:1 respectively.

We found that the mean age was 5.4±3.6 years, similar to the Alhdad study 2011 in Iraq[9] but lower than the Ibrahim study 2011, which reported a mean age of 6.3 years.[6] In this study, the commonest age group was below five years, which was similar to the Al-Hadad study2011[9] and Pedrosa 2007 in Brazil[10] while different than that reported by Faizan 2018 in Pakistan, more than five years.[7]

The mean duration of illness before the presentation was six weeks, slightly higher than Ibrahim's study in 2011 in Iraq, which found that the mean duration of disease before the presentation was 5.2 weeks.[6]

An abdominal mass was this study's most common site of involvement reported in 84.56%. Similarly, many studies found that abdominal mass was the commonest presentation but to lesser percentages ranging from 43.8% in Faizan from Pakistan in 2018,[7] 67.8 % in Ibrahim from Iraq in 2011[6] to 75% in Klumb from Brazil in 2004.[11]

We found that the second most common site of involvement was the peripheral lymph nodes at 20.13%. Ibrahim[6] and Faizan[7] have stated that peripheral lymph nodes were also the second but at higher rates, 27.2 and 37 %, respectively.

In our study, we reported more fever on presentation, 71%, than that reported by Ibrahim,[6] 40%, and Suad[12] in 2008,50.7%. We reported pallor in 49.66%; in Iraq, Ibrahim reported pallor in 46%[6] and Suad in 47.8%.[12]

Splenomegaly was present in 11.4%of patients, lower than in Ibrahim's study, 22.6%,[6] but higher than in Saud study,3%.[12] Hepatomegaly was present in 16.1% of our sample, similar to Saud's study, 14.9%,[12] while lower than in Ibrahim's study, 30.9%.[6] Differences in the rate of reporting hepatosplenomegaly among studies may be due to interpersonal variation in clinical examination or using ultrasound to detect enlarged spleen or liver.

In our study, excisional/incisional biopsy was the most common procedure for the diagnosis, reported in 57.04 %, followed by FNA under US guidance at 38.92%. Ibrahim,[6] in his study conducted in our centre in 2011, showed that FNA was the commonest procedure used for tissue diagnosis, reported in 44%, and the excisional/incisional biopsy in 36.9 %. Diagnosing B-cells NHL using excisional/ incisional biopsy is more accurate than FNA under an ultrasound guide; however, it is more invasive and needs the availability of qualified paediatric surgeons. In our centre, the paediatric surgery services have improved remarkably over the years, so we diagnosed more cases of NHL by excisional/ incisional biopsy than that reported

by Ibrahim in 2011.[6]

The initial Hb level was less than 10 gm/dl in 31.54% of patients, similar to Ibrahim's study in 2011 in Iraq.[6] It has been stated that the limited extent of BM infiltration in NHL usually does not lead to anaemia.[13] The initial WBC count was normal in 63.08% of patients, slightly lower than Ibrahim's study in Iraq in 2011, where the initial WBC count was normal in 70%.[6] The platelet count was low at 3.35 %, similar to Ibrahim's study in 2011 in Iraq, where the initial platelet count was low in only 5.95% of patients.[6] Initial serum uric acid was high at 22.81%; this resembles Ibrahim's study in 2011[6] in Iraq, Ahmed N et al. 2009 in Pakistan[14] and Christy K 2012 in Brazil[15] where serum uric acid was elevated in 29.7%, 30%, and 35% respectively.

In our study, the most common histopathological subtype was BL, 55.70%, which is similar to Ibrahim's study, 58.33%[6] but lower than Ahmed's 2009,[14] Pedrosa's 2007[10] and Guo's 2016 in China[16] where BL and BLL were present in 77.8 %, 78.2%, and 79% respectively. Unclassified NHL was reported in 30.20 % of the patients in our study, higher than Ibrahim's study at 11.3%,[6] Ahmed's study 2009 in Pakistan at 4.2%[14] and Cairo et al 2012 in USA at 8%.[17] The lack of advanced methods of diagnosis like immunohistochemical studies may explain why we have relatively more cases of unclassified NHL. In addition, we depended on FNA under an ultrasound guide to provide the tissue diagnosis in many patients because it is less invasive and usually preferred by the family. It is reported that The sensitivity of FNA in the diagnosis of NHL ranges from 80%-90% and from 67.5%-86% in its subtyping.[18] Diffuse large B-cell NHL was present in 14% of patients, similar to Ibrahim study in Iraq,[6] Klumb et al study in Brazil 2004[11] and Cairo et al study in the USA 2012[17] who found DLBCL were 14.5 %, 11%, and 18% respectively.

Most patients were presented in advanced stages, stage III and VI in 127 (85.23%). Similarly, Ibrahim in 2011 from Iraq[6] found advanced stages in 88 %, Karadeniz from Turkey[19] in 77%, and Christy's study in 2012 from Brazil[15] in 69.9 %. The delay in the presentation and diagnosis might be due to the family and physicians underestimating the patient's symptoms, especially when the symptoms are non-specific, in addition to the aggressiveness of the disease.

Limitation: our study was record-based; its accuracy depends on already registered data. The parameters included are only those found in the record.

CONCLUSION

B-cell Non-Hodgkin's lymphoma is more common in males under five years. The abdomen is the most common site of involvement, and abdominal distension and fever are the commonest symptoms on presentation. Burkitt lymphoma is the most common histopathological subtype and is usually presented in advanced stages.

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Abbreviations list: Anaplastic large cell lymphoma (**ALCL**), Bone Marrow Aspiration (**BMA**), Cerebrospinal fluid (**CSF**), Child's Central Teaching Hospital (**CCTH**), Diffuse large B cell lymphoma (**DLBCL**), Fine Needle Aspiration (**FNA**), Haemoglobin (**Hb**), Hodgkin's disease (**HL**), International Working Formulation (**IWF**), Lactate dehydrogenase (**LDH**), Lymphadenopathy (**LAP**), Lymphoblastic Lymphoma (**LL**), National Cancer Institution (**NCI**), Non-Hodgkin's lymphomas (**NHL**), Statistical package for social sciences (**SPSS**), United States of America (**USA or US**), White Blood Cell (**WBC**) .

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