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ORIGINAL ARTICLE

Clinico-pathological Profile of Childhood Non-hodgkin Lymphoma (NHL) in A Tertiary Care Hospital in Bangladesh

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Abstract

Background: *Non-Hodgkin Lymphoma (NHL) is the third most common childhood malignancy. With histopathology based intensive chemotherapy and CNS-directed therapy, survival can reach more than 80%.*

Objective: *The study was conducted to observe the clinico-pathological findings of NHL in Bangladeshi children.*

Methods: *A prospective observational study was conducted in the Paediatric Haematology and Oncology Department of BSMMU from June 2012 to December 2012. Newly diagnosed NHL patients were included in the study. Patient's initial clinical presentations, time interval from onset of symptoms to diagnosis were recorded. Diagnostic and staging workups were done by CBC, biochemistry, radio-imaging, histopathology (FNAC/excision biopsy), serous fluids/CSF cytology (cytospin), and bone marrow aspiration.*

Result: *Among the 34 patients, BL had preponderance (n=23, 68%) then LL. Median age was 7.6 years. Male: female ratio was 2.1:1. Delayed diagnosis was found in 59% patient. Primary sites were abdomen (65%), thorax (32%), and head-neck (3%). At initial presentation, 83% patients of Burkitt NHL and 100% Lymphoblastic NHL patients came with advanced disease. Bone marrow involvement was found in 23.6% patients and 12% had CNS involvement at their presentation. Irrespective to histology, most common stage was stage-III, which was 53% and then stage-IV was 35%. Median LDH was 1719 U/L. Patient with abdominal variety of NHL came with abdominal complaint like pain (66%), distension (65%), ascites (48%), mass like hepatomegaly (39%), splenomegaly (26%), intussusceptions (8%), testicular involvement (4%). B symptoms were commonly found in 74% patient. Pallor (82%), anorexia, nausea & vomiting (48%), oedema (25%), peripheral lymphadenopathy (49%) were also noticed. In case of thoracic variety of NHL, most common presentation was respiratory distress (90%), superior mediastinal syndrome (SMS) (45%), with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%) with other respiratory finding like chest bulging, mediastinal mass, pleural effusion was also found.*

Conclusions: *About 59% childhood NHL patients tend to present with delayed diagnosis and 88% with advanced disease. Burkitt NHL is the commonest childhood lymphoma, mostly presented with abdominal complaint. Thoracic variety is mostly Lymphoblastic lymphoma. Histopathological findings following excisional biopsy is the most significant and confirmatory for diagnosis. Serum LDH were found significantly high level in both varieties.*

Keywords: *NHL, clinical picture, LDH, diagnostic investigations.*

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Introduction

Childhood NHL is a diverse collection of lymphoid malignancies with varied pathologies, cells of origin, natural history. The history of advances in understanding and management of NHL in the last half of twentieth century is one of the modern success stories of pediatric oncology. Advances in classification, staging, treatment and supportive care have transformed a once invariably fatal disease into one of the most curable childhood cancers.[1] Lymphoma is the third most common malignant tumor in children and adolescent in precedence of leukemia and CNS tumor.[2] It accounts approximately 7% of cancers in less than 20 years of age.[3] The vast majority (70%)[4] are high grade tumors with aggressive clinical behavior.[2,5] NHL comprises a heterogeneous group of lymphoid neoplasm. The distribution of subtypes according to WHO Classification of Tumors of Haematopoetic and Lymphoid Tissues[6] is significantly different in children and adult. In children, Lymphoblastic lymphoma was (LBL/LL) 23%, Burkitt lymphoma (BL) was 60%, and Anaplastic large-cell lymphoma was (ALCL) (17%)[5] while the proportion of Diffuse large B-cell lymphoma (DLBCL) increases with increasing age.[7] Over the last two decades, various studies have shown consistent improvement in overall prognosis.[8] Event free survival (EFS) ranges between 80-90% in B-cell lymphomas,[8-10] and only slightly lowers in LL & ALCL.[11,12] Patient with BM and/or CNS involvement at diagnosis required more intensive therapy and have the worst prognosis.[10,13,14]

Despite its high cure rates in developed countries, the success is not mirrored in resource poor countries. Being a limited resource country, Bangladesh has also inferior survival rates with so many obstacles. Lack of awareness among health care providers for early symptoms of cancer is considered to be the predominant reason for delayed diagnosis with advanced disease, thus resulting inferior outcome and more disappointing treatment result. This study looks into presenting features of childhood NHL of different histopathology in patients who came to BSSMU, and thus helps to share knowledge for early diagnosis among health care professionals and ensures better outcome of our NHL children.

Materials and Methods

This prospective observational study was conducted in the Paediatric Haematology and Oncology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU). Initially total 40 newly diagnosed children with NHL were enrolled from June 2012 to December 2012 but after full filling the exclusion criteria only 34 children were observed for this study. Patients with previous history of malignancy, history receiving chemotherapy or radiotherapy, patients who abandoned treatment in early phase (<5 days), and having predisposing factors like immuno-deficiency, HIV infection, previous transplantation were excluded. For each child a semi-structured questionnaire was prepared; informed written consents were obtained from parents of patients.

All patients were divided into two groups by clinico-histopathological findings (1) Group-A Burkitt NHL (n=24) and (2) Group-B Lymphoblastic NHL (n=11). Histopathological classification was made according to WHO classification for hematological malignancies. As the immunohistochemistry was not available & affordable for all patients; abdominal localizations were included in group for Burkitt lymphoma/B-cell, while those of mediastinal or thoracic involvement were included in therapy group for Lymphoblastic lymphoma/T-cell. They were treated with intensive systemic chemotherapy protocols; LMB-96 protocol for Burkitt group and BFM-95 protocol for Lymphoblastic group.

All patients had undergone for pre-treatment evaluation which included complete history and physical examination, haematological & biochemical investigations including complete blood picture, biochemistry, and coagulation profile. Percutaneous iliac crest bone marrow aspiration for morphological studies and cytospin analyses of CSF were done in every patient to see involvement in these sites. Cytospin analyses of serous fluids were also done in cases of malignant effusions. Imaging studies included chest x-ray, ultrasonography of abdomen and, for some patients, CT-abdomen, CT-chests were done. Patient who had complete resection of tumor were considered as stage-II. But if tumor was not resected or incompletely resected, then they were considered as stage III-IV.

Results

After discarding patients following exclusion criteria, 34 patients were analyzed. Among them 23(67.6%) had BL, 11(32.4%) had LL. Male female ratio was 2.1:1 (BL 2.8:1 and LL 1.2:1). Median age was 7.5 years (range: 2-13 years) for BL 6 years and LL 9 years. Age distribution showed 5-9 years age group

was the commonest, 50% (Table I).

Table I

Patients demographics and characteristics

Traits	Frequency	%	Burkitt Lymphoma (BL) Frequency	%	Lymphoblastic Lymphoma(LL) Frequency	%
No of patients	34	-	23	67.6	11	32.4
Age (years)						
Median	7.5		6		9	
Range (years)	2-13		2-13		5-13	
Age group						
0-4 yrs	7	20.6				
5-9 yrs	17	50				
10-14 yrs	10	29.4				
15-17 yrs	0					
Sex						
Male	23	67.6	17	74	6	54.5
Female	11	32.4	6	26	5	45.5
Male female ratio	2.1:1		2.8:1		1.2:1	
Primary site						
Abdomen	22	65				
Head neck	1	32				
Thorax	11	3				

Most common primary site was 'Abdomen' 22 (65%), next were 'Thorax' 11 (32%) and 'Head-neck' 1(3%) (Table I). On histological basis, all this thoracic variety found LL, abdominal & head-neck region were BL. Irrespective to histology, most common stage was stage-III 53%, and stage-IV was 35%, stage-II was 12% (Fig.-1). At initial presentation, 83% patients of BL came with advanced disease. Most common group was stage-III 43.5%, next stage-IV 39.1% and stage-II 17.4% patients. No patient found in stage-I. On the other hand, 100% LL patients came

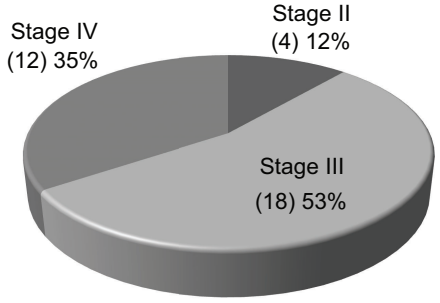

Fig.-1 *Distribution of stage in all childhood NHL (n= 34)*

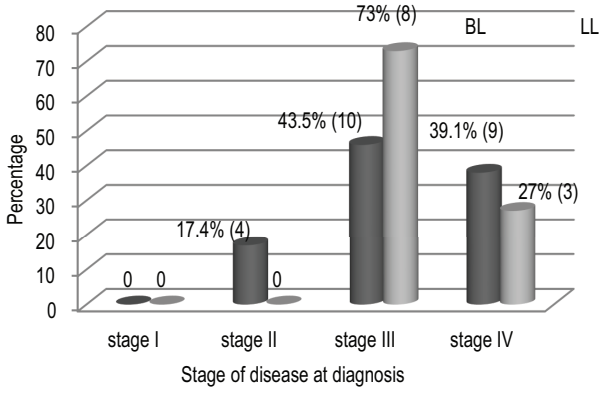

Fig.-2 *Distribution of stage of tumor in different histological sub types of NHL (n=34)*

Table II
Dissemination of childhood NHL at diagnosis (n=34)

Prognostic factor	All patient (n=34)		Burkitt Lymphoma (BL) (n=23)		Lymphoblastic (LL) (n=11)	
	No of patient	Percentage	No of patient	Percentage	No of patient	Percentage
Bone Marrow (BM) involvement						
Yes	8	23.6	6	26	2	18
M2 =5-25% blast	3	37.5	2	33	1	50
M3 =>25% blast	5	62.5	4	67	1	50
No (M1 = <5%blast)	26	76.4	17	74	9	82
CNS involvement						
Yes	4	11.8	3	13	1	9
CNP (Cranial nerve palsy)	1	25			1	100
CSF blast (cytospin)	1	25	1	33	0	0
CNP+CSF blast	2	50	2	67	0	0
No	30	88.2	20	87	10	91

with advanced disease at their initial presentation; stage-III 73% and stage-IV 27%. No patient found in stage-I, II (Fig.-2).

In this study, out of 34 patients, 8 (23.6%) patients had bone marrow involvement. Of them M2 (5-25% blast) was in 37.5%, M3 (>25% blast) was in 62.5% patients. According to histology, 26% of all BL & 18% of all LL had BM involvement at their diagnosis. In case of BL patient M2 found in 33%, M3 in 67% patients. In LL, 50% had M2, 50% had M3 [Table-II]. CNS involvement found in 4(11.8%) patients; of them 25% presented with cranial nerve palsy (CNP), 25% had blast in their CSF, and 50% had both findings together. According to historlogical distribution, 13% of all BL and 9% of all LL had CNS involvement at the time of their diagnosis (Table II).

In this study, definitive diagnosis had been done by histopathology, cytology of serous fluid, and immunohistochemistry. Out of 34 patients, 24 patients were diagnosed by histopathology, of them 10 had excision biopsy & 14 had fine needle aspiration (FNAC). Fifteen patients were diagnosed by cytology of serous fluid (i.e. peritoneal fluid, pericardial fluid) to see malignant cell by cytospin analysis. Immunohistochemistry were done in 8(23.5%) patients with Leucocyte Common Antigen (LCA), CD20, CD3. It revealed 4(11.8%) had B cell (LCA & CD20 positive) and 4(11.8%) had T cell (LCA, CD3 positive). One patient may had more than one method to diagnose the disease

LDH is one of the most important prognostic factors, indicating tumor load at diagnosis. In this study, most patients had high level of LDH in serum (Fig.-3); most common level group was 400-1000 U/L (>2 times above than upper limit of normal) found in 32% patient. Next common group was >4000 U/L (>10 times above than upper limit of normal) found in 21% patients. Median LDH was 1719 U/L, minimum 348 U/L and maximum 8790 U/L.

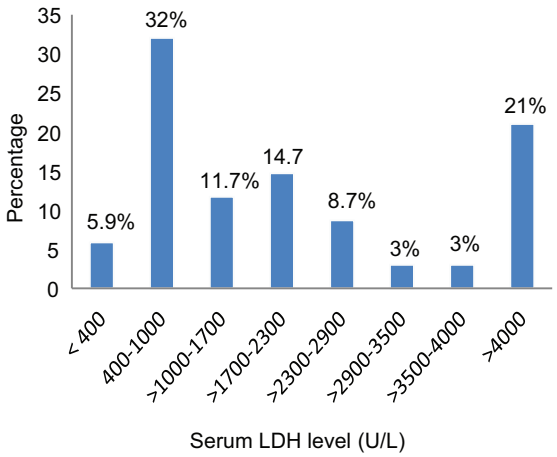

Fig.-3 *Distribution of Serum Lactate Dehydrogenase (LDH) level at diagnosis (n=34)*

Along with abdominal complaint patient with abdominal variety of NHL came with Pallor (82%), B symptoms (74%), peripheral lymphadenopathy (49%), respiratory distress (48%), anorexia, nausea & vomiting (48%) (Fig.-4). In case of thoracic variety of NHL, most common presentation was respiratory distress (90%), with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%) with superior mediastinal syndrome (SMS) (45%), and also hepatomegaly (72%) (Fig.-5).

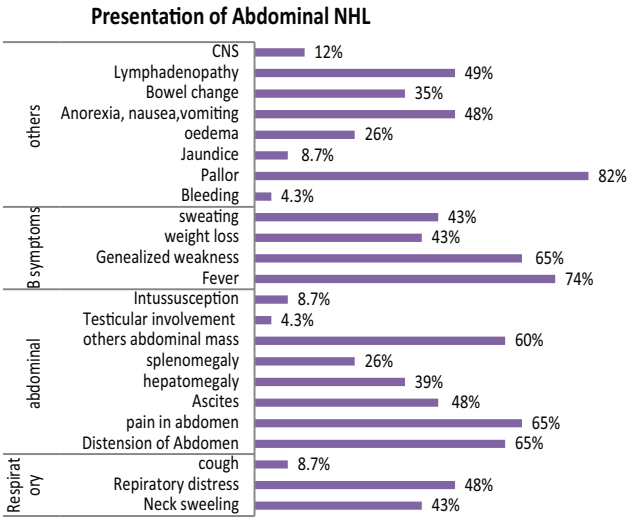

Fig.-4 *Clinical presentation of abdominal variety of NHL*

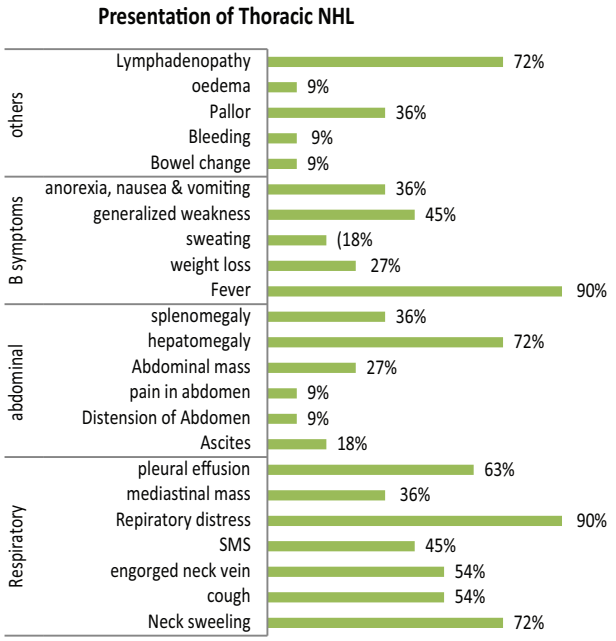

Fig.-5 *Clinical presentation of Thoracic variety of NHL*

A good number of patients (59%) presented with delayed diagnosis (required >30 days from onset of symptoms to diagnosis), 32% came within 4 weeks, and only 9% came early (within <2 weeks) (Fig.-6).

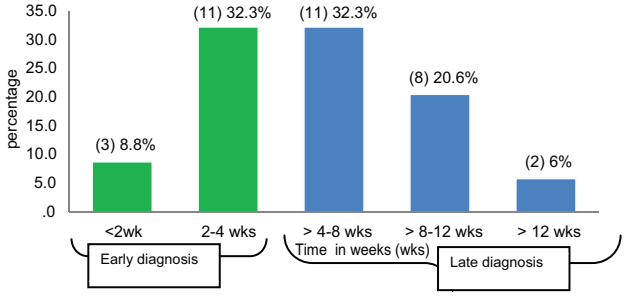

Fig 6 *Time interval between the onsets of symptoms to diagnosis (n=34)*

Discussion

After analysing 34 newly diagnosed childhood NHL patient, it was observed that a good number (38%) patients had delayed diagnosis and so that had delayed start of treatment. It was as like Pedrosa et al[15] study who stated 40% patients had delayed diagnosis and duration of symptoms were on average 50 days. Median age was found 7.5 years, ranging 2-13 years. According to National Cancer Institute (NCI), NHL is rare under 5 years of age but in this study 21% patients were found less than 5 years old at the time of diagnosis. There was no patient under 2 years of age as similar to Sandlund et al[3] analysis. Male were 23 (68%) and female 11 (32%); with ratio 2.1:1.

In this study, primary site of tumor was abdomen in 65%, 32% in thorax and 3% in head-neck region. About 88% patients presented with advanced disease (stage-III, IV) and only 11% presented with localized diseases (stage-I, II). Most common stage was stage-III (53%) and next common was stage-IV(35%). In group observations, all (100%) LL patients and 83.5% of BL had advanced disease. At initial presentation, 23.6% patient came with bone marrow involvement and 11.8% patients had CNS involvement. This result was very similar with the study conducted in St. Jude research hospital by Sandlund et al[16] and Murphy et al[17]. On clinical presentation overview, 96% of BL patients presented with pre-dominantly abdominal disease and 4% in nasopharynx (head-neck region). Sandlund et al[3] also found similar result. Patient came with abdominal complaint like pain (66%), distension of abdomen (65%), ascites (48%), abdominal mass (60%), hepatomegaly (39%), splenomegaly (26%), intussusceptions (8.7%),

testicular involvement (4%). B symptoms were common 74%, respiratory distress noticed in 48% patient. Pallor (82%), anorexia & nausea-vomiting (48%), oedema (25%), peripheral lymphadenopathy (49%) were also noticed. Morsi et al[18] found most common symptom in abdominal NHL was abdominal pain (81.4%), abdominal swelling (76.7%). Martin et al[19] found that, abdominal tumors are associated with abdominal pain, constipation, masses, or ascites. On the other hand, in patient with thoracic variety of NHL most common presentation was respiratory distress (90%), superior mediastinal syndrome (SMS) (45%), mediastinal mass (36%), pleural effusion (63%), along with high incidence of B symptoms (90%), peripheral lymphadenopathy (72%), hepatomegaly (72%). Zhang et al[20] also found mediastinal mass as the most common feature in thoracic NHL.

Due to misdiagnosis, 4 patients were initially diagnosed as TB and treated with anti TB drugs, 1 had steroid therapy before coming here. Five (83%) patient had surgery due to acute condition of abdomen, intussusceptions, abdominal mass before refereeing. In this study, definitive diagnosis of NHL were done by histopathology, cytology of serous fluid and immunohistochemistry. Reiter et al[12] also suggested these investigations to diagnose NHL. With the relation to the histological subtypes, BL was observed to be predominant in this study, affecting 68% patients, rest 32% was LL as like Pedrosa et al[15] studied in Brazil. Elevated serum LDH levels were found in 94% patients, median 1719 U/L, ranges from 348-8790 U/L. Pillon et al[21] found serum LDH 1191 U/L. Although it is non-specific, but it is a good marker of tumor burden and proliferation rate, and has a prognostic value.[9,13] Patte et al[13], Reiter et al[12] studied that treatment should be based on histopathology of tumor mass, and so for this in this study chemotherapy protocol were selected according to histologic subtypes. Here, all BL patients received intensive chemotherapy with 'NHL-FAB-LMB-96' protocol according to their dissemination of disease at diagnosis,[22] all LL patients received chemotherapy with NHL-BFM-95 protocol. Radiotherapy no longer appears to have a role in treatment of primary CNS disease, and radical surgery with its potential risks, has become unnecessary.[13,23-25] So no local/cranial radiotherapy administered in any group of patients and surgery had been done with limitation. For this treatment plan, histopathology plays the most important role.

With the help of major advances in diagnosis, multimodality therapy, development of the rational use of combination chemotherapy and improved supportive care, cure rate of childhood cancer has been increased tremendously. But still now in our country one of the main lacking is delayed or improper diagnosis, this makes patient presented with advanced disease at diagnosis. More the advanced disease the treatment approach and outcome out will be worse.

Conclusion

Childhood NHL is one of the most common malignancy of young age, median age 6 years for Burkitt and 9 years for Lymphoblastic Lymphoma. Usually tends to present with delayed diagnosis with advanced disease. Abdominal varieties were mostly Burkitt lymphoma; revealed B-cell type in immunohistochemistry. They presented with abdominal pain, abdominal mass, ascites, intussusceptions, testicular involvement. Thoracic varieties were commonly Lymphoblastic lymphoma, mostly T-cell type. They usually presented with respiratory distress, superior mediastinal syndrome (SMS), mediastinal mass, pleural effusions. B symptoms, pallor, respiratory distress, peripheral lymphadenopathy were common in both groups. Serum LDH were found significantly high level. Histopathological findings following excisional biopsy is the most significant and confirmatory for diagnosis.

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