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Distribution of Non-Hodgkin Lymphoma in Children and Adolescents. A Study from a Regional Cancer Centre in South India.

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Abstract:
Background*- Non- Hodgkin lymphoma (NHL) is one of the most frequent malignancies in children and adolescents. It represents lymphoid malignancies with diverse clinicopathological and biological features. There are very few studies on the frequency and distribution of NHL in this age group classified according to the WHO classification of 2008.*
A total of 246 cases with lymphoma were diagnosed in pediatric and adolescent patients over a period of five years, of which NHL accounted for 125 cases. The age, gender, anatomical site and distribution of the different subtypes of NHL were analyzed and compared with similar studies.
Result*- The results of our study were comparable to similar studies from India. T-lymphoblastic lymphoma (T-LBL) was the most common NHL. Other common subtypes included Burkitt lymphoma (BL), diffuse large B cell lymphoma (DLBCL) and Anaplastic large cell lymphoma (ALCL).*
Conclusion*- The distribution of different subtypes of NHL is similar to other studies from India and differs from that of other countries.*
Keywords*: adolescent, Burkitt lymphoma, children, lymphoblastic, non -Hodgkin*

I. Introduction

Non –Hodgkin lymphoma is a heterogeneous group of diseases characterized by clonal proliferation of lymphoid cells at various stages of differentiation and accounts for 8-10% of all childhood malignancies. [1] The incidence of NHL has risen dramatically in the last thirty years [2]. A recent study of childhood cancers in South India has shown that lymphomas were the second most common malignancies after leukemia [3].
The aim of this study was to evaluate the frequency and distribution of the various types of NHL in children and adolescents in a regional cancer centre in South India. The pattern and distribution of the various subtypes of NHL were compared with previously published reports from India and other countries. All the NHL cases were classified according to the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues [4].

II. Materials And Methods

This study reviewed the clinical and pathology records of children and adolescents (0-19 years) with the diagnosis of lymphoma between the years 2011-2015 at the Kidwai Memorial Institute of Oncology, Bangalore, which is a tertiary cancer care centre in South India.

A total of 246 patients were diagnosed with lymphoma during this study period. Of these, 50.9 % patients (n=125) were diagnosed as non- Hodgkin lymphoma, 49.1% (n=121) were diagnosed as Hodgkin lymphoma (HL). Clinical information including gender, age and sites of involvement was obtained from case records. The samples consisted of needle and excision biopsies done in our institute and slides and paraffin blocks of cases received from outside centers. Paraffin embedded blocks were cut in to 4-5 µ thick sections and stained with hematoxylin and eosin for morphological analysis. Immunohistochemistry (IHC) was done using the HPR polymer method. The panel of antibodies used for immunohistochemical analysis included monoclonal antibodies to CD3, CD5,CD15,CD20,CD30,CD43,CD45,CD68,CD79a,PAX5,epithelial membrane antigen , cytokeratin, BCL2 protein, cyclin D1, Tdt and Ki- 67 as appropriate. All cases were classified according to the 2008 WHO classification, based on both morphology and immunohistochemistry.

III. Results

A total of 246 patients with lymphoma were diagnosed in the Department of Pathology in the years 2011-2015. NHL constituted 125cases (50.9%) and the remaining 121cases were Hodgkin lymphoma (49.1%). Males were predominantly seen in all types of NHL and the gender distribution of the various NHL subtypes is shown in (**Table 1).** The male to female ratio was 2.8:1 in NHL and 3.09:1 in HL.

3.1 Relative frequencies of NHL subtypes

B cell NHL constituted 68 cases (54.4%) and T cell NHL constituted 57cases (45.6%) of the total 125 NHL cases. Lymphoblastic lymphoma/leukemia was the most common subtype of NHL in this study and comprised 55 cases (44%). This was followed by Burkitt lymphoma with 23cases (18.4%) and DLBCL with 20 cases (16%). Anaplastic large cell lymphoma constituted 14 cases (11.2%). We noted two cases of primary mediastinal large B cell lymphoma and one case each of peripheral T cell lymphoma (PTCL) and subcutaneous panniculitis like T- cell lymphoma (SPTCL). Nine patients could not be classified further and were categorized as B cell lymphoma –unclassifiable. (**Table-1)**

3.2 Distribution of NHL in different age groups

In this study, the youngest patient was two years of age. Sixteen percent of cases were noted between 2-5 years, 28.8 % were seen between 6-10 years, 30.4% were seen between 11-15 years and 24.8 % were seen in the 16-19 year age group.

Among the subtypes, lymphoblastic lymphoma was the most common NHL in the age group of 6-15 years (36/55). Burkitt lymphoma was most frequently seen in the age group of 2-10 years (17/23), DLBCL was seen mainly in the older age group of 11-19 years (17/20). Majority of ALCL were seen in the age group of 6-15 years (8/14). The distribution of the cases in the different age groups is shown in "Fig. 1".

3.3 Sites of involvement

Peripheral lymph nodes were the commonest site of involvement in 56 cases (44.8 %) followed by gastro intestinal tract in 17 cases (13.6%) , mediastinum in 11cases (8.8%), long bones in 7 cases (5.6%) retro peritoneum/intrabdominal region in 6 cases (4.8%) and testis in 5 cases(4%). Other sites included kidney, ovary, urinary bladder, brain and eye (**Table 2).**

IV. Subtypes Of Non-Hodgkin Lymphoma

4.1 Lymphoblastic lymphoma (LBL)

Lymphoblastic lymphoma was the most common NHL subtype (44%) in the present study. The age of patients ranged from 2-19 years with a mean age of 11.3 years and the male: female ratio was 2.4:1.

Of the 55 cases of lymphoblastic lymphoma, T- LBL accounted for 41 cases (74.5%) and B-LBL formed the remainder 25.5%. Peripheral nodes were the most common anatomic sites of involvement for T-LBL with 26 OF 41 cases (63.4%) and B-LBL with 7 of 14 cases (50%). The next most frequent site of involvement for T-LBL was the mediastinum in 10 cases (24.4%) followed by 3 cases in the testis (7.3%) and one case each (2.4%) in bone and kidney. After peripheral nodes, B-LBL involved bone in 4 cases (28.6%), testis in 2 cases (14.3%) and one case involved the skin. All cases with mediastinal involvement were T-LBL.

4.2 Burkitt lymphoma (BL)

Burkitt lymphoma was the second most common NHL subtype. The patients' age ranged from 3-17 years with a mean age of 8.1years and the M: F ratio was 1.4:1. The most common site of involvement was the GIT with 13 cases (56.5%) followed by two cases (8.7%) each in peripheral lymph nodes, retro peritoneum and mandible .One case (4.3%) each in maxilla, tibia, tonsil and urinary bladder was also recorded.

4.3 ALCL

The age range of the patients with ALCL was from 2-19 years with a mean age of 10.9 years and a M: F ratio of 1.7:1. Peripheral lymph nodes were involved in10 cases (71.4%) followed by one case (7.1%) each in skin, bone, brain and orbit. All the cases showed ALK positivity on immunohistochemistry.

4.4 DLBCL

Among 20 patients diagnosed with DLBCL, the age range was 5-19 years, with a mean age of 14.1 years and a M: F ratio of 4:1. Peripheral lymph nodes were involved in 7 cases (35%) followed by three cases (15%) each in bone and GIT. Two cases (10%) involving mediastinum were primary mediastinal large B cell lymphoma (PMLBCL) and there were two cases (10%) of primary CNS lymphoma. One case (5%) each of DLBCL was seen in the eye, maxilla and nasopharynx.

4.5 Other T- cell lymphomas

There was a single case of peripheral T cell lymphoma NOS in a 19 year old male involving peripheral lymph nodes and another unusual case of SPTCL in a 7 year old male child.

V. Figures And Tables

Table1. Break up of different types of NHL in childhood and adolescence (n=125)

Diagnosis	Males	Females	Total	%	M:F Ratio
Lymphoblastic lymphoma	39	16	55	44	2.4
Burkitt lymphoma	19	4	23	18.4	4.75
DLBCL	16	4	20	16	4
ALCL	9	5	14	11.2	1.8
B cell lymphoma unclassified	6	3	9	7.2	2
PMLBCL	1	1	2	1.6	1
PTCL	1	0	1	0.8	
SPTCL	1	0	1	0.8	
Total	18	9	125	100	

Table 2. Sites of involvement of major subtypes of non-Hodgkin lymphoma

Region involved	ALCL		Burkitt lymphoma		DLBCL		Lymphoblastic lymphoma	
	N	%	n	%	n	%	n	%
Peripheral LN	10	71.4	2	8.7	7	35.0	33	60.0
Mediastinum	0		0		1	5.0	10	18.2
GIT	0		13	56.5	3	15.0	0	
Intra-abdomen / Retroperitoneum	0		2	8.7	1	5.0	0	
Skin	1	7.1	0		0		1	1.8
Bones								
a)Long Bone	1	7.1	1	4.3	3	15.0	2	3.6
b)Mandible	0		2	8.7	0		0	
c)Maxilla	0		1	4.3	1	5.0	1	1.8
d)Vertebra	0		0		0		2	3.6
Kidney	0		0		0		1	1.8
Nasopharynx	0		0		1	5.0	0	
Orbital mass	1	7.1	0		0		0	
Ovary	0		0		0		0	
Testis	0		0		0		5	9.1
Brain	1	7.1	0		2	10.0	0	
Tonsil	0		1	4.3	0		0	
Urinary bladder	0		1	4.3	0		0	
Eye	0		0		1	5.0	0	

Table 3. Comparison of major subtypes of pediatric and adolescent NHL in different countries

Major Subtypes	Present Study (<19y)	South India (<_19y)[6]	Western India (<_19y)[7]	Egypt (<_15y)[5]	Korea (<_19y)[8]	Germany (<_19y)[9]
LBL	55(44%)	109(43.2%)	100(34.6%)	26(18.3%)	19(17.8%)	472(22.6)
BL	23(18.4)	56(22.2%)	31(10.7%)	98(16.9%)	25(23.4%)	1004(48.2%)
ALCL	14(11.2%)	29(11.5%)	30(10.4%)	3(2.1%)	22(20.5%)	215(10.3%)
DLBCL	20(16%)	22(8.7%)	72(24.9%)	15(10.6%)	14(13.1%)	173(8.3%)
PTCL, NOS	1(0.8%)	6(2.4%)	4(1.4%)	-	22(8.9%)	

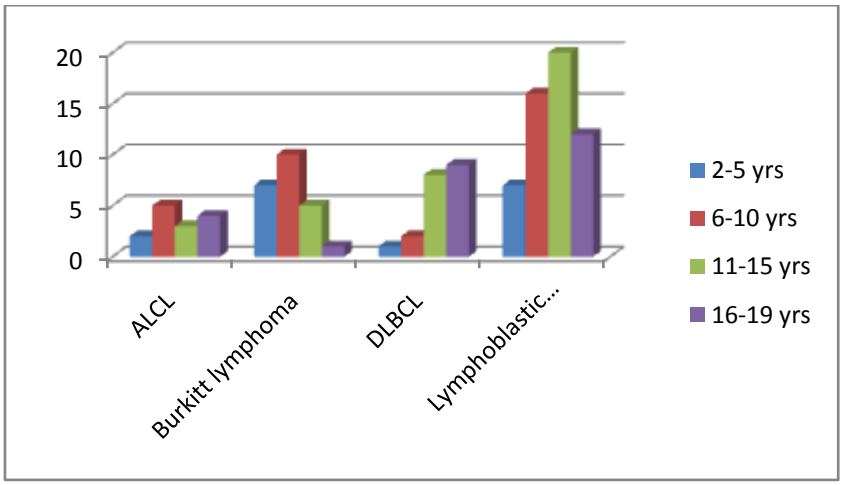

Fig 1.Comparison of the prevalence of different types of NHL among various age groups in pediatric patients

VI. Discussion

NHL is a heterogeneous group of diseases characterized by clonal proliferation of lymphoid cells at various stages of differentiation. NHL accounts for 8-10% of all childhood malignancies [1] and according to a recent study of childhood cancers in South India, lymphomas were the second most common malignancies after leukemia [3].

The NHL/HL ratio in our study was 1.03:1, indicating an almost equal incidence of NHL and HL, in contrast to the Western literature where the ratio is 1.5:1[10]. Similar to our results a reduced ratio of NHL: HL was also noted in other Indian studies, where Swaminathan et al [3] reported a ratio of 0.89 and Manipadam et al [6] a ratio of 1.2:1.

The male: female ratio of our study was 2.8:1which was similar to ratios of 2.87:1 and 2.5:1 in the two other studies reported from India [1, 11]. A similar M: F ratio was also noted in the Western literature with Wright et al [12] reporting a ratio of 2.7:1 and Pedrosa et al [13] reporting a ratio of 2.4:1. All the major subtypes of NHL in our study showed a male predominance. The highest M: F ratio in our study was seen in Burkitt lymphoma 4.75:1 and the lowest ratio was seen in ALCL among major subtypes.

In our study the youngest patient was two years of age. Sandlund *et al* [1] and Manipadam *et al* [6] reported that the incidence of NHL increased uniformly with age and was rarely diagnosed before 2 years.

Majority of our patients were in the age group of 6-15 years constituting 59.2% of cases. Sixteen percent of patients were in the age group of 2-5 years and 24.8% belonged to the age group of 16-19 years. These findings are similar to another study from India by Manipadam et.al where 56.4% of patients belonged to the age group of 5-14 years and 12.3% of patients were seen in less than five years of age. These results are in contrast to a study from Brazil in which 48.2% of patients were under five years of age [13]

Though LBL cases were seen in all age groups, the majority (65.5%) were seen between 6-15 years. Most cases (73.9%) of BL were seen under the age of ten years whereas the majority (58.8%) of ALCL was seen in the older age group of 16-19 years. Most DLBCL (85%) cases were seen between 11-19 years. These findings are similar to the studies in India [1] and the USA [14]

Peripheral lymph nodes were involved in 55 cases (44%) followed by GIT and Intrabdominal/retro peritoneum in 22 cases (17.6%). These findings are similar to an earlier Indian study in which peripheral nodes were involved in 48% of cases and GIT & intrabdominal/retroperitoneum were involved in 18.2% of cases [6]. In contrast, in a study by Sherief et al, the abdomen was the most frequent site (73.2%) of involvement by NHL in Egypt [2] which may be because of the high incidence of Burkitt lymphoma in African countries.

Lymphoblastic lymphoma was the commonest NHL and comprised 44% of all cases in our study. T - lymphoblastic lymphoma was the commonest subtype and this constituted 32.8 % of all NHL cases which is similar to the other studies of India where it constituted 32.1% and 32.0% by Manipadam et al [6] and Srinivas et al [7].In contrast, the incidence of T-LBL is low in Western studies constituting 19% in UK [12] and 16.1% in Germany [9]. The reason for the high incidence of T-LBL in India is not certain. A possible role of various environmental and genetic factors is considered [15, 16, 17, 18], though the exact reason remains elusive.

Burkitt lymphoma was the second most common lymphoma and constitutes 18.4% of all NHL cases. This is unlike the findings reported from Brazil, Kuwait, Saudi Arabia, Germany and Egypt which accounted for 78.2, 77.2, 68, 48.2, 42.2 and 39 % of the cases [13, 19, 20, 9, and 5]. Reports from Pakistan and Shanghai show a low frequency as do the studies from India [21, 7]. The commonest anatomic site of BL in our study was GIT, which was in contrast to other studies of South India [6], where it was seen predominantly in intrabdominal/ retroperitoneal region. In our study, involvement of jaw bones was slightly higher (13%) as was observed in an

earlier study from the same centre [22] whereas other studies from India have a low incidence of jaw involvement.[6,7].

In our study DLBCL was the third most common sub-type and constituted 16% of all NHL cases. This is in contrast to other studies from Korea [8], Germany [9], and UK [12], which showed 13.1%, 8.3% and 3.3% of DLBCL in all NHL cases. One study from Western India [7] showed a higher percentage (24.9%) whereas another South Indian [6] study showed a lower percentage (8.7%) of DLBCL among all NHL cases. There were two cases of PMLBCL in our study. Pediatric DLBCL have a better prognosis as most of them belong to the germinal centre B cell phenotype [23].

We also had a high incidence B cell unclassified lymphoma (7.2%), as high grade DLBCL can sometimes be difficult to distinguish from BL even after IHC. In our series this category included both cases of BCL-U with features intermediate between DLBCL and BL and some cases which could not be further categorized, as a complete panel of IHC could not be done due to financial constraints.

ALCL was the fourth most common subtype and constituted 11.2% of all NHL cases. This result is similar to studies from India [3, 6], Germany [9], and UK [12] whereas studies from Korea [8] reported a higher percentage (20.5%). All 14 cases in our study were ALK positive.Two cases of PTCL constituted 1.6% of all NHL, of which one was a case of PTCL NOS and the other was SPTCL. The incidence of PTCL in our study was similar to a study from UK [12] where it accounted for 1.6% of NHL in patients less than 14 years of age. It was lower when compared to the other study from South India [6]. We also encountered a rare case of SPTCL in a seven year old boy.

In conclusion, we studied the distribution of different subtypes of NHL in children and adolescents in a tertiary cancer care centre. All the cases were IHC proven and classified according to the 2008 WHO classification. We compared our data with other published data from India and other countries. The incidence of NHL was almost equal to that of HL in this age group and T- Lymphoblastic lymphoma was the commonest among all subtypes of NHL. The gastrointestinal tract was the commonest anatomical site for Burkitt lymphoma.

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