Non-Hodgkin Lymphoma (NHL) in Children: an Epidemiologicial Analysis of NHL in Children in Albania during 2003-2012

Healthcare

Keywords: NHL, lymphocyte, chemotherapy, UHC, group age, epidemiological data, histological type.

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Abstract

INTRODUCTION: Non-Hodgkin lymphoma (NHL) refers to a group of diverse tumors derived from cells of lymphocytic lineage. They occur as clonal proliferation of single cells at any stage of lymphocyte development. Sixty percent of all childhood lymphomas have been classified as non-Hodgkin's lymphoma, representing 8% of all childhood malignancies. In contrast to adult NHL, childhood NHL are typically high grade, they tent to present as advanced disease, yet with intensive multiagent chemotherapy, the outcome is favorable. THE AIM: The aim of the study was to analyze the demographical, epidemiological data of the Non-Hodgkin's lymphomas in the time period 2003-2012. METHODOLOGY: The study is a retrospective describing type, taken from January 2003 to December 2012 (a 10 year study). In this study, there were included data from cartels of the Pediatric Oncohematology the ward Hospital Center "Mother Teresa" in Tirana. In our country this service is unique, providing that our data can be considered with a national character. THE RESULT: In the study, there were involved a total of 53 patients. From that, 36 (67.9%) were male and 17 (32.1 %) female. The most affected age, was group age of 11-14 year olds and the group age with the lowest was 0-3 year olds. The most frequent clinical type was abdominal type 30/53 (56.6%) and the most frequent histological type was Burkitt's lymphoma 47.2 %. THE CONCLUSION: NHL, in our study is ranked in third place 8.6% after leukemia and brain tumors. In children, this disease is of a more aggressive type. This suggests a preventive campaign in the health education of the parents, the necessary information of the family doctor and the regional hospitals in order to have an earlier diagnosis. The future continues to be bright for increasing the long-term survival rate and decreasing the acute toxicity and long-term morbidity in children with both limited and advanced stage of the non-Hodgkin's lymphoma.

Introduction

The lymphomas are malign neoplasms with an origin from the lymphoid tissue. They are part of a large group of the diseases called the hematological neoplasms. They begin and develop as a result of the genetic aberrations which influence in the proliferation, the differential and cell apoptosis. The malign non –Hodgkin's lymphomas are heterogenic groups of neoplasms which derive from the origin of lymphocyte cells. They happen as a clonal proliferation of a single cell in each faze of the differentiation of the lymphocyte.

The lymphomas are clinically, pathologically and biologically distinctive. They include more than 60 clinical-pathological entities which are divided in the maturity and origin forms. The difference is related to the type of the lymphocyte included, so called the origin cell: B-Cell, T-Cell, the Natural Killer cells.

Epdemiology

The malign lymphomas which include the Morbus Hodgkin and the Non- Hodgkin's lymphomas (NHL) make up 15 % of all the malign diseases in children.

Sixty percent of all childhood lymphomas have been classified as non-Hodgkin's lymphomas, representing 8% of all childhood malignancies whereas the other part is of the Hodgkin lymphoma.

This disease can appear in every age during childhood but before the age 3-5 is rare. The incidence is stable in children below the age of 15, but a light growth in those of 15- 19.

Non-Hodgkin's lymphomas have a higher incidence in males than females. The male to female ratio is 2.7:1.

NHL is almost twice more common in white children than the colored ones.

Ten percent of the children with born or gained immunodeficiency can develop the NHL.

Geographical Differences in the Incidence of Lympoid Neoplasms in Children

Childhood lymphomas occur throughout the world, although the relative frequency of non-Hodgkin's lymphoma varies markedly from country to country. In Equatorial Africa, for example, approximately 50 % of childhood cancers are lymphomas, and this markedly increased frequency is the consequence of the very high incidence of Burkitt's lymphoma in this region. Lymphoblastic and large cell lymphomas also occur in Equatorial Africa, probably with a similar incidence to that in the more developed countries. The Burkitt's lymphoma is more common in the Latin America, North Africa, Middle East in comparison with USA and Europe. The incidence of the Burkitt's lymphoma in the equatorial Africa is approximately 100 for 1 million children under the age of 15 compared to 2 million, under the age of 15 in the North America.

The endemic form of NHL is associated to the Epstein - Barr virus (EVB) (carry of EVB genomes in their cells) in the 95 % of the cases towards the sporadic form which is related to EBV only in the 15 - 20 % of the cases.

Etiopatogeneses

Many authors accept the existence of various factors which separated or in collaboration with one- another can induct in a neoplastic disorder. Some of the factors are:

Genetic Mutations
Constitutional Factors
Viruses
Ionizing Radiation
Organs Transplant
Chemical Agents

Biology and Cytokinetic

B-cell lymphomas in childhood
They express: IgM, CD19 and CD20, HLA-DR.
They do not contain the enzyme terminal deoxyribonucleotide transferase (TdT), antigen CD5.
Antigen CD10 is present on the surface of pre-B cells.
T-cell lymphomas in childhood
Lymphoblastic lymphoma with T- Cell: contain the enzyme TdT which serves to make the difference of the lymphoblastic lymphoma from the Burkitt's lymphoma. Express antigens CD7, CD5. HLA-DR is rarely.
Anaplastic lymphoma: Express antigen CD30. Express interleukin-2 receptor and HLA antigens. Some of these tumors express a mixture of T- and B-cell markers, and some bear no recognized surface markers of the T- and B-cell lineages.

Childhood lymphomas are all rapidly growing neoplasms with very high growth fraction. B-cell tumors have the highest growth fractions.

Genetics Pathology

B-cell lymphomas in childhood: In the Burkitt's and Burkitt's-like lymphomas usual translocation is (8; 14) in the region (q24-q32). The breakpoints in the involved chromosomes coincided with the location of a proto-oncogene involved in cellular proliferation (c-myc on chromosome 8, band q24), and it was soon shown that the c-myc gene is translocated from chromosome 8 to the heavy chain locus on chromosome 14. This leads to disorganization of the c-myc express and incontinent increases of the cellular proliferation.
Other translocations in the Burkitt's lymphoma include (2; 8) (p12; q24) and t (8; 22) (q24; q11).

The translocation t (14; 18) (q32; q21) occur in the Diffuse large cell lymphoma. The result of this translocation is the disorganization of the gene bcl-2 which blocks the apoptosis inhibition.

T-cell lymphomas in childhood: Proto-oncogene tal-1 which is placed in the chromosome (1p34) normally is silent and as a result of the translocation t (1, 14) (p34; q11) it is activated playing a part in the lymphagenesis, in the lymphoblastic lymphoma with the T-cells.

Also, the translocation t (2; 5) (p23; q35) is specific for anaplastic large cell lymphomas. This results in the fusion of the involved genes (the amino-terminal portion of the nucleophosmin gene, NPM, on chromosome 5 with the catalytic domain of the Anaplastic lymphoma kinase gene, ALK, on chromosome 2) resulting in a new proteinic product.

The Systems of Classification

The latest version of the classification according to WHO is based in:

1.Immunophenotype
2.Clinical presentations
3.Molecular pathology
4.Genetics pathology

Based on histological characteristics, NHL is being divided in LNH with B and T cells.
The National Cancer Institute (NCI) according to histology sets NHL three main categories:

1.Small Noncleaved Cell Lymphomas (Burkitt's and non-Burkitt's)
2.Lymphoblastic Lymphomas
3.Large Cell Lymphomas

Stages Of NHL in Children

Stage I
A single tumor (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen
Stage II
A single tumor (extranodal) with regional node involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm
A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable

Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
Any primary intrathoracic tumor (mediastinal, pleural, or thymic)
Extensive primary intraabdominal disease
Any paraspinal or epidural tumor, whether or not other sites are involved

Stage IV
Any of the above findings with initial involvement of the central nervous system, bone marrow, or both

*Based on the classification proposed by Murphy.

Clinical Presentations
The clinical presentation of the childhood Non-Hodgkin's lymphomas is mainly depending on the histological subtype and the stage of the disease.
The frequency of the involvement according to primary sites and tumor distribution at the time of diagnosis has been noted to be as the follows: the abdomen 35 percent, the mediastinum 26 percent, head and neck 13 percent, peripheral nodes 14 percent and other sites (including bone, epidural space, breast, gonads, orbit, and skin) 11 percent.

Small Noncleaved Cell Lymphoma (Burkitt's and non-Burkitt's)

The children with the endemic form (in the equatorial Africa) commonly present with head and neck involvement, including, most specifically jaw involvement and less commonly abdominal and paraspinal diseases.

Children with sporadic type (in North America and Europe) will commonly present with abdominal involvement that is manifested by abdominal pain, nausea and vomiting, and signs of acute intestinal obstruction.

Children with CSN involvement often present with spinal cord compression, cranial and /or peripheral nerve palsies, and /or seizures and require immediate clinical attention.

Lymphoblastic Lymphomas
Childhood lymphoblastic lymphoma is often manifested with a mediastinal mass (50% up to 70%) and often with bilateral pleural effusions and hepatosplenomegaly.
Childhood lymphoblastic lymphoma may also involve and can spread to the bone marrow and/or the CNS.

Children presenting more than 25% of the lymphoblastic lymphoma cells in the bone marrow are often diagnosed and treated as acute lymphoblastic leukemia (ALL) and treated on ALL treatment protocols.

Large Cell Lymphomas

Diffuse Large B-cell lymphomas: it is presented similarly to other forms of B-cell small noncleaved-cell lymphoma. There is an increases incidence of the mediastinal involvement in B-large versus B-small noncleaved-cell lymphoma.

Anaplastic large cell lymphomas (Ki-1): in a typical way it involves the skin, CNS, lymph nodes, lungs, tests, and muscles as well as the gastrointestinal tract.

Diagnosis

The diagnostic evaluation for the patients with lymphoprolipherative diseases should include:

1. History and physical examination
2. Complete blood count
3. Viral Test: HIV, HTLV-1; Hepatitis B and C
4. Biopsy of the peripheral lymphadenopathy (excisional biopsy)
5. Bone marrow aspiration and biopsy
6. Cytological examination
7. Immunohistochemical analyses of biopic material
8. Immunophenotypic analysis
9. Cytogenetic and molecular analysis
10. Lumbar Puncture in order to see the spread of CNS (brain and spinal cord).
11. The Ultrasound examination
12. Chest radiography
13. Chest CT scan for mediastinal, hilar nodes and pulmonary parenchymal infiltration
14. Abdominal and pelvis CT for lymphadenomegaly, splenomegaly, hepar and lien pathology
15. MRI
16. Bone control
17. PET scan

Treatment

Chemotherapy: The primary modality of treatment for all histological types and stages of childhood non-Hodgkin's lymphoma is multiagent chemotherapy.

Surgery: Surgery has a limited role in the treatment of NHL in children. Surgery can be used in the case when the tumor is small and located and it is totally resectable.

Radiotherapy: Ro-therapy has also a limited use. Ro-therapy can be used in emergency cases, in life threatening complications like the superior vena cava syndrome and the involvement of the SNQ.

Biotherapy: Rituximab is a monoclonal chimeric antibody, target toward the antigen CD 20, approved from the FDA for the treatment of NHL with B cells combined with the CHOP protocol.

The therapy with Interferon: The therapy with Interferon interferes in the diminishing or stopping the progress of some types of NHL.

Target therapy: The monoclonal antibodies and the inhibitor of tyrosine kinase are two types of the target therapy which are used in the treatment of NHL.

Bone marrow transplantation: Autologous, allogeneic or from the umbilical cord.

Complications of Therapy

Complications with potential risk are:

- Superior vena cava syndrome
- Acute tumor lysis sindrome
- Other complications less common include: pericardiac tamponade, obstructive jaundice, intestinal obstruction, intestinal perforation, neurological deficiency, nephropathy from the uric acid etc.

Prognosis

The prognosis for childhood and adolescent NHL has improved dramatically in the last 30 years. The estimated 5-year event-free survival (EFS) for the childhood and adolescent NHL ranges from 60% to 100% after multiagent chemotherapy.

The first and second stages patients of this disease have a perfect prognosis, despite the histology.

The advanced stage has a survival nearly 60-75%, whereas for the refractor or recurrent forms the survival diminishes to 40-60%.

The prognosis, however, for children and adolescents with NHL who relapse and\ or have a progressive disease, is dismal with an estimated 10% to 30% overall survival. These patients are considered as candidates for an allogeneic transplant of the bone marrow.

The Future Consideration

Future approaches need to be developed to reduce both acute and long-term toxicities without reducing the recent improvement in long-term disease-free survival. Further investigation into the molecular and genetic etiologies and/or association with specific subtypes of childhood non-Hodgkin's lymphoma should be a major area of future pursuit. An increased understanding of the molecular abnormalities associated with childhood non-Hodgkin's lymphoma will enhance the development of specific molecular targeted therapy, including antisense gene therapy. A second major area of investigation should include the development of new forms of immunotherapy. It is possible that the target therapy can substitute some chemo-preparations that actually are needed to cure NHL at an early age in an advance stage. The future continues to be bright for increasing the long-term survival rate and decreasing the acute toxicity and long-term morbidity in children with both limited and advanced stage non-Hodgkin's lymphoma.

The Aim of the Study

The aim of the study was to analyses the demographical, epidemiological data of the Non-Hodgkin's lymphomas in order to gain information during a 10 year period (January 2003- December 2012).

The Specific Study Objectives

- Theoretical basic knowledge of the diseases
- Knowing the clinical sign frequency, the histological type, the staging classification of LNH in the pediatric ages
- The analyses of the demographic, epidemiological data for the LHN in children
- The identification of the possible correlations among some epidemiology parameters. And also, with the clinical form, histology and stages.

Methodology

Type of study: The study is retrospective and describing type. In this study there were included data from cartels of the Pediatric Oncohematology ward in "Mother Teresa" Hospital Tirana. The data involved in the study were analyzed in a descriptive way according to some variables (demographical, geographical, related to the living place) in order to know the models of this pathology in the pediatric ages.

The population in study: In the study there were involved 53 children of the age 0 to 14 year olds with the Non-Hodgkin's lymphomas diagnosed, treated and attended in the Pediatric Oncohematology ward, (there have been excluded the cases from Kosovo.)

Period of study: The cases of study belong to a period of 10 years (January 2003- December 2012).

- The samples characteristics
- Number of cases: 53
- Median: 96 month or 8 year
- Mode: 12, 14
- The standard deviation: 3.87

Data and analyses collection

The received data were placed in a special survey.

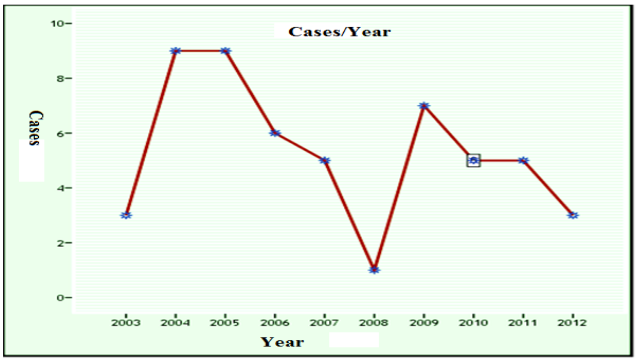
The data was organized in a database in excel and then imported in the program "The Statistical Package for the Social Sciences" SPSS Version 20.0 and the statistical analyses was made there.

The Results

The dynamic study: It resulted with not significative statistical changes which do not give ultimate conclusions in relation to the increase or decrease of this dynamic. The dynamic study, divided into 5 year periods gives evidence for a higher result in the period 2003-2007.

Table 1: The dynamic of NHL during a 10 year of the study (January 2003-December 2012)

Year	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	**Total**
Cases	3	9	9	6	5	1	7	5	5	3	53
Percentage	5.7	17	17	11.3	9.4	1.9	13.2	9.4	9.4	5.7	100



Graph 1: The dynamic of NHL during a 10 year of the study (January 2003-December 2012)

Table 2: The dynamic of NHL divided into 5 year periods

DYNAMICS OF NHL IN TWO PERIODS					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2003-2007	**32**	**60.4**	**60.4**	**60.4**
	2008-2012	**21**	**39.6**	**39.6**	**100**
	Total	**53**	**100**	**100**	

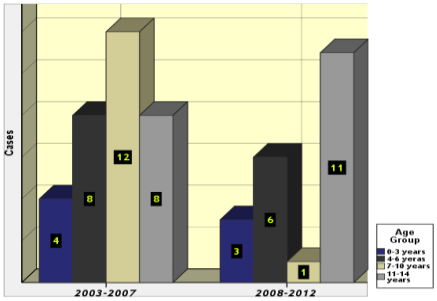
Gender Study: The gender study gives evidence of a higher percentage in male 36/53 (67.9%) from 17/53 (32.1 %) the case of female patients. In both periods of study, (2003-2007 2008-2012) the frequency remains higher in male.

Graph 2: The dynamic of NHL divided into 5 year periods

Table 3: The male to female ratio during a 10 years of the study

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F	17	32.1	32.1	32.1
	M	36	67.9	67.9	100
	Total	53	100	100	

Age study: Before the age of 2 we have not a single case, this is based even in documents which refer a low incidence before the age of 2. The rarity of NHL under the age of 2 suggests that the environment exposure can be important in the pediatric lymphomas. Around the age of 12 and 14 we have a higher frequency of cases. The frequency of NHL in the age groups 0-3, 4-6 , 7-10 , 11-14 year olds resulted in the highest numbers in the age group **11-14 year olds and lowest number in the age group 0-3 year olds**. During the period (2003-2007) dominates the age group 7-10, whereas (2008-2012) dominates the age group 11-14 year olds.



Graph 3: Distribution of cases according to age group in two periods of the study

Table 4: Cases of NHL according to four group age

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0-3 YEAR	**7**	**13.2**	**13.2**	**13.2**
	4-6 YEAR	**14**	**26.4**	**26.4**	**75.5**
	7-10 YEAR	**13**	**24.5**	**24.5**	**100**
	11-14 YEAR	**19**	**35.8**	**35.8**	**49.1**
	Total	**53**	**100**	**100**	

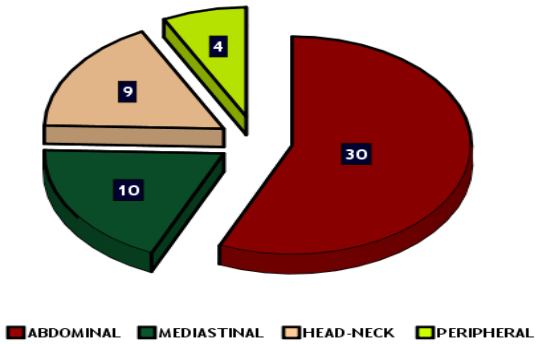
Geographical study: The results present differences between the regions, resulting zero in some places such as : Delvina, Devolli, Hasi, Mirdita, Kukësi, Saranda etc. and in some other places there is a large number of cases in places such as Tirana, Durres, Dibër, Shkoder, Fier etc.

Table 5: Distribution of cases of NHL in children according to 12 prefectures

PREFECTURE					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BERAT	**2**	**3.8**	**3.8**	**3.8**
	DIBER	**8**	**15.1**	**15.1**	**18.9**
	DURRES	**8**	**15.1**	**15.1**	**34**
	ELBASAN	**3**	**5.7**	**5.7**	**39.6**
	FIER	**6**	**11.3**	**11.3**	**50.9**
	GJIROKASTER	**5**	**9.4**	**9.4**	**60.4**
	KORCE	**3**	**5.7**	**5.7**	**66**
	KUKES	**1**	**1.9**	**1.9**	**67.9**
	LEZHE	**1**	**1.9**	**1.9**	**69.8**
	SHKODER	**5**	**9.4**	**9.4**	**79.2**
	TIRANE	**10**	**18.9**	**18.9**	**98.1**
	VLORE	**1**	**1.9**	**1.9**	**100**
	Total	**53**	**100**	**100**	

Clinical forms study: The distribution according to the clinical forms is mainly in the abdominal form, where from 53 cases of study, 30 cases or 56.6 % belong to the abdominal form. In the second place is the Mediastinal form with 10 cases or 18.9 %. The Head-Neck form is in the third place with 9 cases or 17 %, whereas the Peripheral form is in the fourth place with 4 cases or 7.5 %.

There is a decrease of the Abdominal and Head-Neck forms from the first period (2003-2007) to the second one (2008-2012). The abdominal form stands above all the age group, whereas the mediastinal form dominates more in the age group 11-14 year olds.



Graph 4: Distribution of clinical forms

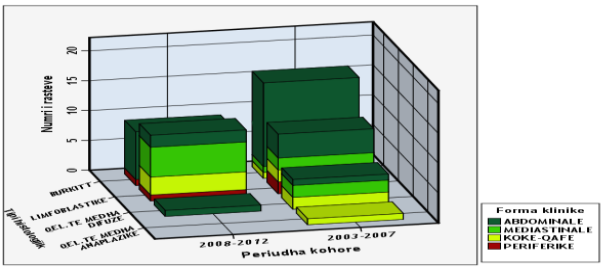
Table 6: Distribution of clinical forms of NHL in children during a 10 year of the study

CLINICAL FORMS					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ABDOMINAL	**30**	**56.6**	**56.6**	**56.6**
	HEAD-NECK	**9**	**17**	**17**	**73.6**
	MEDIASTINAL	**10**	**18.9**	**18.9**	**92.5**
	PERIPHERAL	**4**	**7.5**	**7.5**	**100**
	Total	**53**	**100**	**100**	

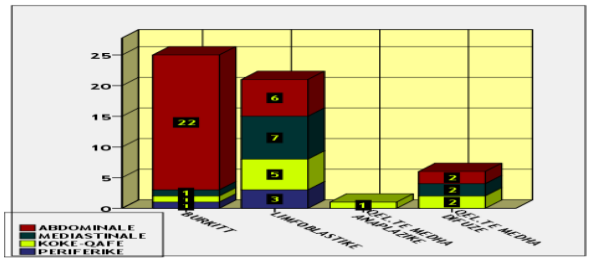
The histological type Study: The histological type distribution is led by the Burkitt's lymphoma with 47.2 %, followed by the Lymphoblastic Lymphoma with 39.6 %, in the third place stands the Diffusive Large Cell Lymphoma with 11.3 % and in the last place it is the Anaplastic Large Cell Lymphoma with 1.9 %. In the period (2003-2007) dominates the Burkitt's lymphoma, whereas in the period (2008-2012) dominates the Lymphoblastic lymphoma. There is a growth association of the Burkitt's lymphoma with the abdominal form and the Lymphoblastic lymphoma with the mediastinal form. It is being seen that the four histological types of lymphomas result in a larger number of the cases in the older age groups, predominating with the lymphoblastic lymphomas.

Table 7: Distribution of four histological types in children

HISTOLOGICAL TYPES					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BURKITT	**25**	**47.2**	**47.2**	**47.2**
	LYMPHOBLASTIC	**21**	**39.6**	**39.6**	**86.8**
	DIFFUSE LARGE CELL	**6**	**11.3**	**11.3**	**88.7**
	ANAPLASTIC LARGE CELL	**1**	**1.9**	**1.9**	**100**
	Total	**53**	**100**	**100**	

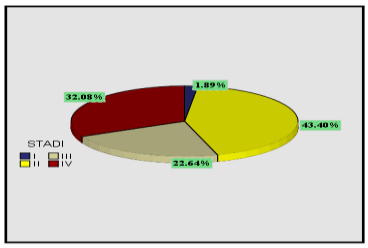


Graph 5: Correlation between histological types and clinical forms in two periods



Graph 6: Correlation between histological types and clinical forms

The stages study: The first (I**)** stage results very decreased confront the data of other authors. The second (II) stage has the higher percentage with 43.4%, followed by the fourth (IV**)** stage with 32.1 % and later with third (III**)** stage with 22.6 %. The abdominal form appears in the high number of cases in the second stage, followed by the third and the fourth. Whereas mediastinal form appear in the most part of the cases in fourth stage. Knowing that the abdominal form is in most part of the cases Burkitt's lymphoma with B-Cell, while the mediastinal form present in the major part the lymphoblastic lymphoma with T-Cell, this explains once more the higher aggressiveness of the T-Cell toward B-Cell.



Graph 7: Staging classification of NHL in children

Conclusions

From the dynamic study of the NHL some differences were noticed which do not give conclusions of the increase or decrease of this dynamic. The frequency of the NHL remains higher at males. The age group with a higher number of cases was 11-14 and the lowest number the age group 0-3 year olds. The study of the cases according to the geographical regions resulted with a higher of cases in Tirana, Durres, Dibër, Shkoder, and Fier. The most frequent clinical form was the Abdominal form (56.6 %), followed by the Mediastinal form (18.9 %), the Head –Neck form is in the third place (17 %), in the end it results the Peripheral form (7.5 %). The most frequent histological type is led by the Burkitt's lymphoma (47.2 %), followed by the Lymphoblastic Lymphoma (39.6 %), in the third place results the Diffusive Large Cell Lymphoma (11.3 %) and in the end results the Anaplastic Large Cell Lymphoma (1.9 %). The second stage resulted in a higher percentage (43.4 %), followed by the fourth stage (32.1 %) and then by third stage (22.6 %). The first stage results very decreased (1.9 %).

Recommendations

The dynamic study of the NHL can be challenging for searching the predisposal, environmental or other factors that may have influenced in the appearance of the disease in that period of time. The study of NHL of a higher frequency in male is recommended in screening campaign for an earlier diagnosis. The geographical distribution study in some regions with a higher percentage leads to the search of the predisposal factors in order to decrease or elimination their oncologic effect. The clinical form analyses and the frequent histological type lead to a therapeutic plan. The analyses of the study which shows that this disease in children is of an aggressive type, suggests a preventive campaign in the health education of the parents, the information of the family doctor and regional hospitals for an earlier diagnosis.

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