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ORIGINAL PAPER

Etiological and Clinical Characteristics of Lymphadenopathy at Child Age in Tuzla Canton

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Lymphadenopathy is defined as an abnormality in the size or character of lymph nodes, is caused by the invasion or propagation of either inflammatory cells or neoplastic cells into the node. Numerous factors, such as age, localization, size and consistency, present and previous pathological conditions are very important in order to define the future diagnostic and therapeutic course. **Objective:** The aim of this study was to determine the etiological and clinical characteristics of lymphadenopathy in children in the area of the Tuzla Canton. **Patients and Methods:** This retrospective–prospective study analyzed the medical records of the Department of Pediatrics in Tuzla of 334 patients in age from 0 to 14 years, in which the clinical signs of palpable lymph nodes of one or more regions was diagnosed in the period from January 1st 1998 to June 30th 2003. The anamnesis data, clinical findings, diagnostic procedures results, therapeutic approach and disease outcome etiology defined lymphadenopathy were analyzed. **Results:** Out of 334 children, localized lymphadenopathy have been verified in 230, and generalized in 104. Male/female ratio was 1:1.8. Final results of our study have shown the etiologies as following: Infectious etiologies, 79.34%, neoplastic 11.34%, and non-neoplastic 9.28%. In neoplastic etiologies, lymphoblastic leukemia has been the most often verified neoplastic disease (68.4%), not related to the age or sex of patient, and equally presented as localized and generalized lymphadenopathy. In this study lymphomas were presented by generalized lymphadenopathy. **Conclusion:** The regional and generalized lymphadenopathy in children depends on their etiology and has significant prognostic value for the disease. **Key words:** lymphadenopathy, etiology, childhood

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1. INTRODUCTION

Lymphadenopathy is a common diagnostic and therapeutic problem in pediatrics (1). Almost all children develop lymphadenopathy at least once during childhood, usually in response to various infections (2). Localized lymphadenopathy is most commonly caused by an infectious agent, and generalized forms are often part of the diagnostic-therapeutic and prognostic unfavorable conditions (3). Distribution of the enlarged lymph nodes compared with characteristics depending on the anatomical localization and age-related reference values, it can often give basic guidelines for the establishment of differential diagnosis and determining the etiological causes (4). The etiology of increased lymph nodes may have clinical and diagnostic significance. Because of the wide spectrum of causes of lymphadenopathy is easier and more acceptable to discuss them within the categorization of lymphadenopathy, or discuss the causes of generalized and regional lymphadenopathy. Generalized lymphadenopathy is defined as an increase of more than 2 groups of interrelated groups of lymph nodes (5). In the literature there is very little data on the incidence of lymphadenopathy in children and is generally considered part of certain pathological conditions or within individual etiologic factors.

The clinical picture of lymphadenopathy is neither unique nor simple. Depends, above all, the etiological factors and age of the patient. According to the agent and the appearance of involved lymph nodes symptoms and clinical findings could be divided into several categories according to the local and general symptoms and signs. Due to the width of etiological agents, symptomatology in children is almost individual.

The study was undertaken in order to determine the etiology of diagnosed lymphadenopathy in relation to age and sex, and distribution of regional and generalized lymphadenopathy in relation to the etiology and the time period examined.

2. PATIENTS AND METHODS

The retrospect–prospective study included children of both sexes, aged 0-14 years, in which there were clinical signs of palpable lymph nodes of one or more regions, which were hospitalized

in the Clinic for child diseases in Tuzla in the period from January 1st 1998 to June 30th 2003. Total number of respondents was the 334.

From the medical records were analyzed anamnesis data (personal and family history), clinical findings, laboratory tests (ESR, complete blood count, transaminases, copper, and beta2mikroglobuline), microbiological tests (swabs of throat and nose), serological analysis of the Ebstein Barr virus (EBV) and cytomegalovirus (CMV), radiological examination of the thorax, ultrasound of the neck and abdomen, and cytological and histopathological tests results.

3. STATISTICAL ANALYSIS

In the statistical analysis of data obtained were used the standard descriptive measures, and measures of central tendency (mean), absolute measures of dispersion (variance and standard deviation). To test the statistical hypothesis, we used one-way tests. When testing a hypothesis based on one sample, we used z-test for testing hypotheses about the proportion of the basic set. When testing a hypothesis based on two samples, we used z-test for testing hypotheses about the different proportions of two sets.

4. RESULTS

From a total of 334 children, 116 (34.73%) were girls and 218 (65.27%) boys. The ratio of girls and boys was 1:1.8. In relation to the total number of treated children, we found that lymphadenopathy was significantly more often diagnosed in boys than girls. The average age of the children studied was 6.72 years (δ±4.02) and 7.03 (δ± 3.93) year for girls and 6.56 (δ± 4:05) G. for boys.

Regardless of gender, in relation to age, lymphadenopathy in children have only partly similar curve trends and impressions, which shows that the age of 2 to 4 years in both sexes is an important risk period with nearly identical intensity and dynamic of reporting. After that age, age 80-10 year and 11 to 14 years in girls represents another significant spike in verified lymphadenopathy. Whatever the cause, boys have slightly larger fluctuations and a substantial rise in verified lymphadenopathy occurrence only in the prepubescent age (Figure 1).

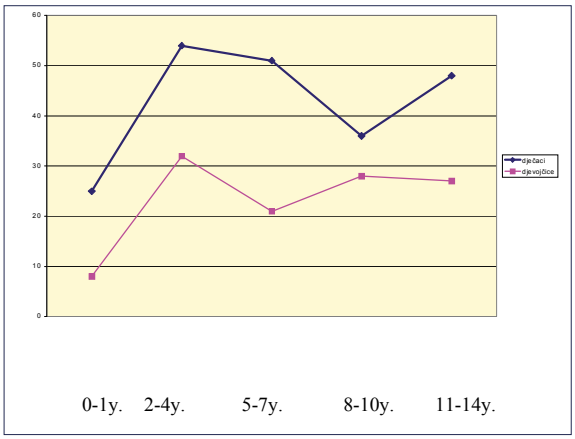

Figure 1. Distribution of lymphadenopathy in relation to age

In 230 (68.86%) cases there was regional, and in 104 (31.14%) generalized lymphadenopathy and statistics showed that lymphadenopathy in our study was significantly more likely to manifest as a regionally in relation to the generalized ($Z = 6.91 > Z\alpha = 0.05 = 1.64$).

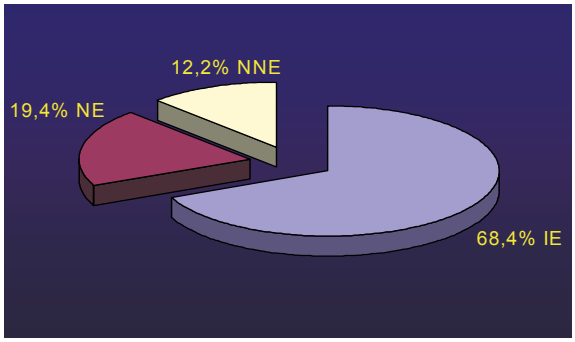

Figure 2. The etiology of generalized lymphadenopathy

Infectious etiology (IE) is the dominant cause of lymphadenopathy in children in our study. Infectious diseases as a cause of lymph nodes enlargement in children with continuing significant presence in all the years of analyzed period, show a marked spike in 2000 which was followed by a linear decline in frequency. The overall representation of infectious agents are highly significant factor ($Z = 10.693 > Z\alpha = 0.01 = 2.33$) in the occurrence of lymphadenopathy in children. Neoplastic diseases of children ages have a uniform appearance of the dynamics, while factors non neoplastic etiology with two spikes in 2001 and the first six months of 2003 account for more than 67% of verified cases.

Within regional lymphadenopathy, as well as the overall representation, an infectious etiology with the 198 (84.08%), makes a significant factor in the development of lymphadenopathy, followed by less frequent, neoplastic etiology with 19 (8%) and non neoplastic etiology with 19 (8%) cases. In the infectious etiology of regional lymphadenopathy bacteria are significantly more common cause in relation to viruses and parasites, with very high significance level ($Z = 4.986 > Z\alpha = 0.01 = 2.33$). Significantly, there is still high share of Mycobacterium tuberculosis (29.85%) in the etiology of infection and parasites, Toxoplasma gondii is the sole cause of verified regional lymphadenopathy.

Region	1998	1999	2000	2001	2002	2003
Cervical	9	18	16	9	8	5
Mediastinum	5	14	10	5	5	-
Supra clavicular	-	-	1	-	-	-
Axillary	5	1	3	4	2	2
Inguinal	5	4	8	2	2	4

Table 1. Representation of certain regions of generalized lymphadenopathy of infectious etiology in the examined period

The regional lymphadenopathy infectious etiology cervical lymph nodes are a series of mostly the affected region, followed by mediastinal, axillary and inguinal regions.

By analyzing the neoplastic etiology of regional lymphadenopathy, we found that most verified malignant disease of children ages regardless of gender and age is lymphoblast acute leukemia, while other malignancies have relatively uniform incidence of neoplastic processes that manifest by regional lymphadenopathy in children at our Canton over 90% of cases lead to the increase of cervical lymph nodes.

Non neoplastic etiology presented a mixed picture of different conditions that directly–or indirectly by spreading disease–a reactive response, leading to

enlargement of lymph nodes. Largely verified, etiologic non neoplastic state, the result of reactive changes in lymph nodes, such as sinus histiocytosis, cysts, non-specific granulation, situations after the vaccine...

In generalized lymphadenopathy infectious etiology was significantly more often represented with 68.4% (Figure 2). As in the regional and generalized lymphadenopathy in the etiology of infection is usually represented by a bacterial etiology with 67.16%, followed by the virus as the cause of 31.34%. Mycobacterium tuberculosis as the most frequently identified bacteria in 64.4% cases, cause a significant ($Z = 01.93 > Z\alpha = 0.05 = 1.64$) generalized lymphadenopathy, while 38.1% with EBV usually verified by a virus.

Within the generalized lymphadenopathy of infectious etiology cervical and mediastinal lymph nodes is mostly affected region, which followed, axillary and inguinal regions (Table 1).

Acute lymphoblast leukemia was evenly represented in all the years of analyzed period, both manifests as regional and generalized lymphadenopathy, while lymphomas in children aged manifest only by generalized lymphadenopathy.

Generalized lymphadenopathy due to expansion of neoplastic process, primarily involves enlargement of cervical lymph nodes and mediastinal region. Representation of others and the relationship of other regions depend on the type of malignant processes. Supra clavicular and abdominal enlargement of lymph nodes is characteristic of epithelial tumors of the stomach and bowel cancer (1 case), and abdominal inguinal combination was found in Wilms tumor. Involvement of more than two regions is generally characterized by a primary neoplasm of lymphoid tissue.

5. DISCUSSION

Due to the large number of different diseases that can lead to enlargement of lymph nodes to determine the true cause in children can be difficult. Therefore, in the diagnostic evaluation of lymphadenopathy in children should pay attention to the increased localization of lymph nodes, abnormal values in a complete blood count (CBC), abnormalities in the x-ray image (radiograph) of individual regions, and abnormal ultrasound findings. In the above, one of the most important is the size of lymph nodes in relation to the child's age. In healthy children lymphoid tissue is slightly enlarged after birth until the age of 8 to 12 years, after which it gradually decreases during puberty, and continues to decline throughout life. Bilateral palpable lymph nodes in the neck region up to 2 cm can be found in children with previously verified upper respiratory tract infections. Almost 50% of children aged less than 2 years have palpable lymph nodes of the neck. Although, more than 25% of malignant tumors in children are found exactly in this region, less than 2% of palpable nodes are malignant. However, in children, each lymph node in the neck, larger than 1 cm should be considered as lymphadenopathy. Axillary nodes to 1 cm and inguinal up to 1.5 cm in diameter in older school-age children are usually common finding in children aged 7 years requires monitoring, and for infants from 2 months are the indications for diagnostic testing. The presence of even a particle supra clavicular nodes (<0.5 cm) regardless of age, are always a reason for further detailed diagnostic evaluation and are often associated with malignancy (6). In patients with lymphadenopathy in primary care, prevalence of malignant etiology is only 1.1. Key factors that speak in favor of malignant etiology include older age, regardless of age, they are hard, fixed lymph nodes that persist for longer than two weeks, and have supra clavicular localization. Lymphadenopathy may be the only clinical sign, or one of the few non-specific symptoms of the disease. Knowing and recognizing these factors is crucial in the treatment of vague lymphadenopathy whose follow-up can last up to a month, after which a biopsy is the method of choice to diagnose its etiology. A wide range of causes, which lead to enlargement of lymph nodes are easily categorized and remembered using the mnemonic acronym "MIAMI" meaning: Malignancies; Infection, Autoimmune disorders, Miscellaneous and unusual conditions (7). The exact incidence of lymphadenopathy, regardless of age, is not known, and is usually considered within individual etiologic factors. One of the few studies of population which gives valid results is the Danish study which reported an annual incidence of 0.6% lymphadenopathy in the general population. According Reddy in 25% of biopted lymph nodes was verified the secondary malignancy, and 20% of cases it is a primary malignant tumor of lymphoid tissue (8). In the United States malignant etiology and autoimmune diseases in children are much less common cause of lymphadenopathy in relation to infectious etiology (6).

In relation to the total number of children (334) with verified lymphadenopathy in our study, 79.34% had infectious etiology, 11.34% had neoplastic etiology, and 9.28% non neoplastic etiology. Very similar results were presented by the Granada and co-authors who found infectious etiology in 81% of verified cases of lymphadenopathy in children, and neoplastic in 16% (9). The percentage of malignant etiology is basically very low in children but increases with age. The largest part of detected lymphadenopathy in children is infectious or benign in etiology, with a history of short duration and mainly regional.

In our study, in 230 cases it was a regional, and 104 generalized lymphadenopathy. In the literature there is little data dealing with the problem of comparative representation and manifestation of diseases of regional or generalized lymphadenopathy. Therefore, very detailed, and above all well directed history is essential to further determine the etiology of lymphadenopathy. Particular attention should be paid to immunization status of the child and the accompanying reactions. The distribution of lymphadenopathy is usually drained in the evaluation of certain diseases. Within regional lymphadenopathy, usually infectious etiology was present with 198 (86.08%) cases, followed by considerably less common, neoplastic etiology and non neoplastic etiology

with the 19 (8%).

Physical characteristics of the enlarged lymph nodes are very important in defining the possible etiology. With infection, the affected lymph nodes are asymmetrically enlarged, tense, discretely interconnected, and erythematosus skin over. Nodes affected by metastatic cancer usually are hard and fixed. Nodes enlarged neoplastic lymphoid proliferations are usually solid, non-presstresed and interconnected (10). Careful palpation of the submandibular, front and rear of the cervical, supra clavicular, axillary and inguinal regions in a simple, fast and non-aggressive way of a preliminary differentiation between regional and generalized lymphadenopathy. According to literature data, the most affected region in the infectious etiology is cervical, followed by inguinal and axillary regions (7,10). These data are entirely consistent with our results, which show a slightly more often affected mediastinal region. Although a significant number of cases are relatively quickly diagnosed and successfully treated, some entities, such as atypical mycobacterium, cat-scratch disease, toxoplasmosis, tuberculosis, leading to persistent lymphadenopathy over several months, which can be replaced by malignant processes (7). Our results show that bacterial infections in children treated at the Clinic of Pediatric Diseases, University Clinical Centre Tuzla, and the most common cause of lymphadenopathy of one or more regions. In addition to streptococcal and staphylococcal bacteria, Mycobacterium tuberculosis is 29.85% of regional lymphadenopathy primary cause of disease, while in generalized lymphadenopathy her presence even more significant ($p>0.05$). A retrospective study of Moore and colleagues, involving biopted lymph nodes from 1332 children aged less than 15 years, with the manifest lymphadenopathy, showed the presence of granulomatous inflammation in 36.3% of cases, while tuberculosis lymphadenitis was confirmed in 54.5%. A higher proportion of tuberculosis detected in this study compared to our study may be explained by the long period of time in which the study was conducted (1976-1999), but it certainly confirms the high prevalence of tuberculosis in the last decade (11). In support of this view speak the Tygerberg study with 23.6% of verified tuberculosis of cervical lymph nodes, and a study conducted in Nigeria with 32.7% of TB in children (12,13). Recent studies indicate that in developing countries, the expected annual risk of tuberculosis infection in children is 2.5%, with a marked increase in the number of tuberculous lymphadenitis in the last two decades (14). Data from the same studies indicate that children mortality tubercular etiology is responsible in 8-20% of cases, depending on the health and social standards of the country. According to the World Health Organization, only in the United States (U.S.), as a developed country, the incidence of tuberculosis has declined by 13% in all age groups during the period from 1985 to 1994, but the percentage of disease among children under 15 years is increased by 33% (15). In the verified bacterial etiology of lymphadenopathy dominated by streptococcal and staphylococcal infections, particularly in children older than 3 years. Group A streptococcal infection, with consequent adenopathy are actually associated ailments of school children, especially in spring and autumn (16). Staphylococcus aureus (37%) and group A streptococci (16%) from the study by Trobs and colleagues almost entirely reflects the bacterial flora verified in our material in the presence of some other much less represented in mixed infections (17).

It is interesting that in the infective etiology, and regional, particularly generalized lymphadenopathy (31.34%) in the examined period, are the viruses which caused increased lymph nodes in children are significantly represented. Within a viral etiology in particular has a significant role EBV and is usually verified in generalized viral lymphadenopathy (38.1%). This is somewhat higher than in the study by Benesch and associates (23%), conducted at the Child and the pediatric clinic of the University of Gratz (2). Such a difference in the prevalence of EBV among our respondents in relation to the Austrian study may explain the still present a number of migrations to the region, as well as poor socioeconomic conditions, especially in the returnee and refugee settlements.

The etiology of malignant disease of childhood that we verify, acute lymphoblast leukemia is usually verified disease (68.4%), regardless of gender and age of the child, which equally manifest as regional and generalized lymphadenopathy. Generalized lymphadenopathy at the time of diagnosis was present in 70% of children with ALL and in 31% of children with AML, as in the case of ALL, which almost completely agrees with our results. Among sick children in our study lymphomas manifest only by generalized lymphadenopathy, while literature data are mainly from developed countries, give opinion that the lymphomas in children are more often manifested by regional lymphadenopathy (6). In children older than 6 years, dominated by non-Hodgkin and Hodgkin's lymphomas, which are in 80-90% of cases of Hodgkin's associated with cervical lymphadenopathy, as opposed to 40% of non-Hodgkin associated lymphadenopathy. Until 7 age of the disease occurs more frequently in boys (10:1), and after the 12 years of age of incidence is approximately equal in both sexes (1,1:1) (18).

In the study by Moore and associates which considered the diagnostic aspects of cervical lymphadenopathy in children 2/3 of 154 patients with neoplastic altered and enlarged lymph nodes had lymphoma, a further 10 had lymphadenopathy associated with leukemia (19). The study also reported more Tygerberg lymphoma (Hodgkin's/non-Hodgkin's lymphoma–33%/23.5%) than leukemia (5%). In our experience, the leukemia is more often verified malignant disease (45.16%) than lymphoma (19.35%). Although it has been verified by a small number of lymphoma in the analyzed period, as in other studies of Hodgkin's lymphoma aged children are more common than non-Hodgkin (9,12). According to data of Bergeron, the occurrence of lymphoma there is a slight male predominance in the age of 15 years, while the incidence of occurrence in this age of about 5.5 cases per million children (20). In our study of 6 verified lymphoma, 2 were diagnosed in boys and at the ages of 11 and 11.5 years, while other were girls at the age of 8, 1 and 13.5 years.

Other diagnosed malignancies are mostly single cases of malignant tumors (neuro blastoma, Wilms tumor) are typical for children's age, or tumors whose incidence has its peak to adult age (melanoma and colon cancer), and whose appearance in children is certainly a consequence of additional genetic mutations. Sills and colleagues have put forward the fact that these tumors are most common in the first 6 years of age, as confirmed by our results, and to 27% just manifested lymphadenopathy of the head and neck (6). Cervical series of lymph nodes and in our material are usually the affected ones. Neoplastic processes that manifest by regional lymphadenopathy in children in our study in over 90% of cases, leading to enlargement of cervical lymph nodes, and generalized lymphadenopathy primarily involves the cervical lymph nodes enlargement, then mediastinal, inguinal and axillary regions. Representation of other regions depends on the type of malignant processes of the primary tumor. Malignant process in the lymph nodes usually provides a solid, less mobile and connected to the lymph nodes. Very careful palpation is essential to the differentiation of benign reactive lymph nodes due to frequent inflammation may be fibrotic and firm.

Viral illnesses (such as EBV, adenovirus, enterovirus, herpes virus, and CMV) frequently cause lymphadenitis and lymphadenopathy. Together with bacterial infections that affect the drainage of lymph nodes, giving similar symptoms and appearance of the lymph nodes. Usually there is a case of "warm" nodes which are the size of 2-6 cm, erythematosus skin over them, warm, tense and sometimes fluctuating. "Cold" nodes are usually a reflection of sub acute or chronic inflammation, are less tense and not warm. They are not accompanied by suppuration so it is difficult to distinguish them from simple non inflammatory enlargement of lymph nodes. Lymphomatous lymph nodes are usually non-presstresed, symmetric, rubbery, mobile, and usually 1.5 to 2 cm in diameter. Metastatic infiltrated lymph nodes are mainly nonpresstresed, extremely hard, large, and immobile and fixed to the substrate.

The diagnostic evaluation must be determined and guided by clinical evaluation, but it certainly needs to include certain laboratory analyze, microbiology, serological, radiological examination and other diagnostic procedures such as cytological and histopathological analysis (5).

6. CONCLUSION

The clinical picture of lymphadenopathy in children is neither simple nor uniform, which is why the diagnosis is very complex and demanding, with a very different etiology and requires almost an individual approach. It is precisely these data which underscore the need for improved of diagnostic methods, development of effective therapies, control of clinical trials, as well as improving supportive care for patients.

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