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ACUTE LEUKEMIA OF CHILDHOOD - A SINGLE INSTITUTION'S EXPERIENCE

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Abstract - The aim of this study was to investigate distribution of immunophenotypic and cytogenetic features of childhood acute leukemia (AL) in the cohort of 239 newly diagnosed patiens registered at the leading pediatric oncohematology center in the country during a six-year period (1996-2002). With approximately 60-70% of all childhood AL cases in Serbia and Montenegro being diagnosed and treated in this institution the used data represent a valid research sample to draw conclusions for entire country.

On the basis of five phenotypic markers, the distribution of immunological subtypes was as follows: 169 (70.7%) expressed B-cell marker CD19 (137 were CD10 positive and 32 CD10 negative), 37 (15.5%) belonged to T-lineage acute lymphoblastic leukemia (T-ALL) (cyCD3 positive), and 33 (13.8%) were acute myeloblastic leukemia (AML) (CD13 positive and/or CD33 positive in the absence of lymphoid-associated antigens). The ratio of males and females was 1.5:1. Most of the cases were between the ages of 2 and 4, and were predominantly B-lineage acute lymphoblastic leukemia (B-ALL) cases. Another peak of age distribution was observed at the age of 7. The frequency of T-ALL (18% of ALL) was similar to that reported for Mediterranean countries: France (19.4%), Greece (28.1%), Southern Italy (28.3%), and Bulgaria (28.0%). Cytogenetic analyses were performed in 193 patients: 164 ALL and 29 AML. Normal karyotype was found in 57% of ALL and in 55% of AML patients, while cytogenetic abnormalities including structural, numerical, and complex chromosomal rearrangements were found in 43% of ALL and in 45% of AML patients. Our results represent a contribution to epidemiological aspects of childhood leukemia studies.

Key words: Acute leukemia, childhood, hemopathology, Serbia and Montenegro

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INTRODUCTION

The acute leukemias, the most frequent type of childhood cancer in developed countries, are a heterogenous group of diseases with regard to type, treatment response, prognosis, and (probably) etiology as well (Parkin *et al.* 1998; Pui, 1999). This variation, combined with the relative rarity of the diseases, compromises epidemiological studies aimed at identifying causal associations. Etiological clues could (however) be derived from comparing national incidence rates. Incidence rates of AL, its age dependence, and geographic variations within the different subgroups might be linked with socioeconomic status and concomitant exposure to potential leukemogenic agents (Greaves *et al.* 1993; Ramot and Magrath, 1982). As a contribution to such epidemiological studies, we here present systemized data on the distribution of immunophenotypic and cytogenetic features of AL subgroups in Serbia and Montenegro. The research is based on cases registered at the Department of Oncohematology's Pediatric Clinic of the Mother and Child Health Institute of Serbia in Belgrade. The department is the leading pediatric oncohematology center in the country. With approximately 70% of all childhood AL cases in Serbia and Montenegro being diagnosed and treated in this institution, the used data represent a valid research sample from which to draw conclusions for the entire country.

PATIENTS AND METHODS

Patients and immunophenotype

From October 1996 to May 2002, AL was diagnosed in 260 patients admitted to the Mother and Child Health Institute of Serbia. Immunophenotyping was performed on a series of 250 previously untreated patients, and successful results were obtained in 239 of them. The expression of CD19, CD10, cytoplasmic CD3 (cyCD3), CD13, and CD33 antigens was assessed by the alkaline-phosphatase/antialkaline-phosphatase (APAAP) method (Erber *et al.* 1986; Erber and Mason, 1985). All monoclonal antibodies as well as the APAAP kit were purchased from Dako (Dakopatts, Glostrup, Denmark).

Morphological, cytochemical, and cytogenetic analyses

All cases met the conventional morphological and cytochemical criteria (Sudan BB and ANAE) for the diagnosis and were further classified according to the FAB system (Van den Does-van den Berg *et al.* 1992; Benett *et al.* 1976). Cytogenetic analysis was performed on bone marrow cells after direct preparation and/or unstimulated 24-48 h short-term culture. At least 20 metaphases were analyzed for each case, using conventional cytogenetics with GTG banding.

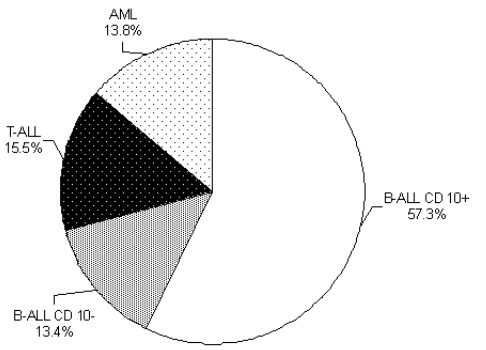

Fig 1. Distribution of immunophenotypes of childhood AL in 239 patiens in Serbia and Montenegro

RESULTS

Immunophenotypic studies

The distribution of immunophenotypic subclases according to age and sex for 239 AL patients is shown in Table 1. Among them, 169 (70.7%) expressed the B-cell marker CD19 (137/169 were CD10 positive and 32/169 CD10 negative), 37 (15.5%) belonged to T-ALL (cyCD3 positive), and 33 (13.8%) were AML (Fig. 1). The subclass distribution of ALL is reported in Fig. 2: 66.5% were B-ALL CD10+, 15.5 % were B-ALL CD10-, and 18% were T-ALL. The ratio of males and females is given in Fig. 3; there were 144 male (60%) and 95 female (40%), patients, giving a male:female ratio of 1.5:1. Males predominated in all groups, but the difference is most striking in T-ALLs (male:female ratio - 3.6:1). For AML the sex ratio is closer to unity.

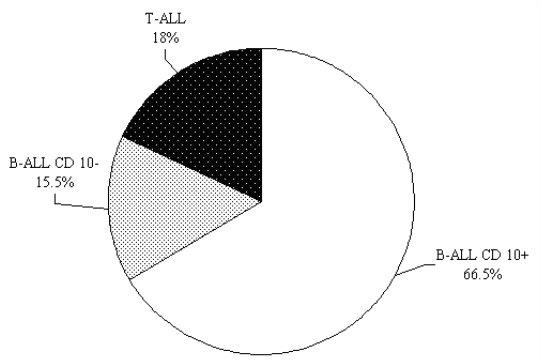

Fig. 2. Distribution of immunophenotypes of childhood ALL in 206 patiens in Serbia and Montenegro

Age-related distribution of AL patients

The age distribution is shown in Fig. 4. The median age for ALL was 5 (range: 4 months to 17 years) and for AML 7 (range: one day to 16 years). The overall peak of incidence was between the ages of 2 and 4. This peak was formed predominantly by B-ALL CD10+, which represented 87% of all cases in this age group, where another peak at the age of 7 was observed. After the age of 7, the proportions of B and T subtypes were similar. The peak incidence of T-ALL was between the ages of 8 and 13. We noticed a bimodal distribution of AML with major peaks at the ages of 1 and 8.

Cytogenetic studies

Cytogenetic analyses were performed in 228/239 (95%) of AL patients: 196/206 (95%) ALL and 32/33 (97%) AML patients. Successful results were obtained in 193/228 (85%) of AL patients: 164/196 (84%) ALL and 29/32 (90%) AML patients (Table 2). Among 164 ALL patients, a normal karyotype was found in 93/164 (57%) patients: 57/93 (61%) B-ALL CD10+, 10/93 (11%) B-ALL CD10-, and 26/93 (28%) T-ALL. We found that 71/164 ALL patients (43%) had an abnormal karyotype:

Table 1. Age and sex distribution of immunophenotypes of childhood AL in 239 patients in Serbia and Montenegro

Age group (years)	ALL-B CD10+		ALL-B CD10-		ALL-T		AML	
	Male	Female	Male	Female	Male	Female	Male	Female
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
<1	2 (1)	1 (1)	1 (3)	4 (13)	0	0	1 (3)	3 (9)
1-5	44 (32)	35 (25)	7 (22)	4 (13)	4 (11)	2 (6)	8 (25)	4 (12)
6-10	16 (12)	14 (10)	8 (25)	3 (9)	15 (40)	3 (8)	4 (12)	3 (9)
11-17	16 (12)	9 (7)	3 (9)	2 (6)	10 (27)	3 (8)	5 (15)	5 (15)
Total	78 (57)	59 (43)	19 (59)	13 (41)	29 (78)	8 (22)	18 (55)	15 (45)
	137 (100)		32 (100)		37 (100)		33 (100)	

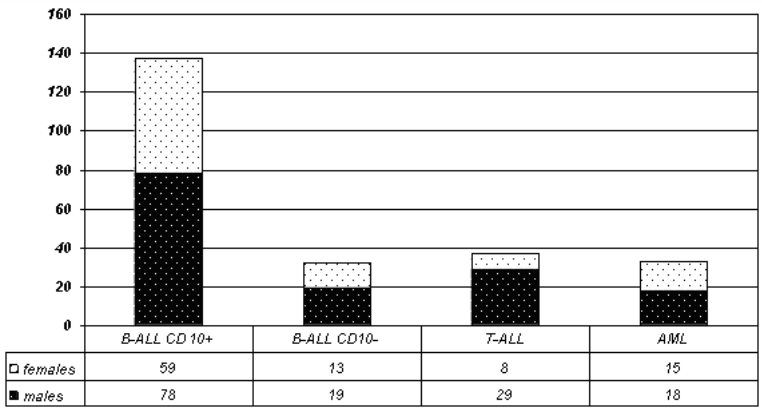

Fig. 3. Ratio of males to females in 239 childhood AL patients in Serbia and Montenegro

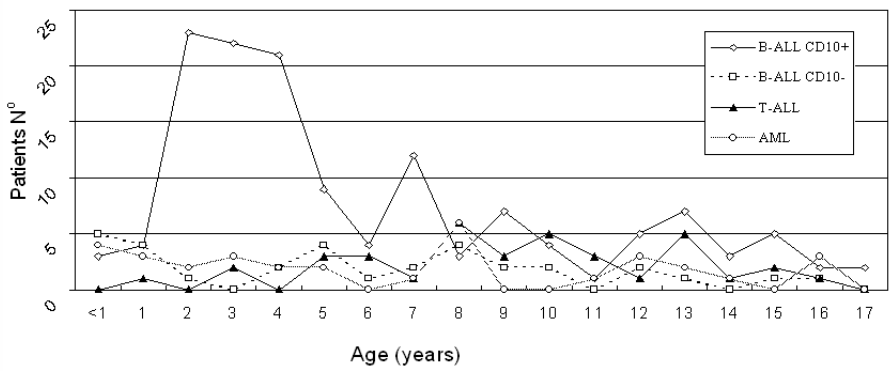

Fig. 4. Age-related distribution of childhood AL in 239 patients in Serbia and Montenegro

52/71 (73%) B-ALL CD10+, 13/71 (18%) B-ALL CD10- and 6/71 (8%) T-ALL. Numerical aberrations were found in 36/71 (51%) patients: 33/36 (92%) B-ALL CD+, and 3/36 (8%) B-ALL CD-. Among them hyperdiploidy (47-57) was present in 26/36 patients (24 B-ALL CD10+, 2 B-ALL CD10-); near triploidy (58-80) in 8/36 patients (7 B-ALL CD10+, 1 B-ALL CD10-); and near tetraploidy (92±) in 2/36 patients with B-ALL CD10+. Structural aberrations were detected in 18/71 (25%) ALL patients; and 7/18 (39%) B-ALL CD10+, 10/18 (56%) B-ALL CD10-, and 1/18 (6%) T-ALL. Among seven B-ALL CD10+, three patients had t(9;22)(q34;q11); while inv (1)(p34;q21), del (9)(p13), der (1), and der (3), were present in one patient each. In 10 B-ALL CD10-, the following structural aberrations were found: t(8;14)(q24;q32), t(4;11)(q21;q23), t(1;11)(p32;q23), and t(13;19)(q14; p13), one patient each; dup (1)(q21; q32) in two patients; and der (1), der (9), der (18), and der 19 in one patient

each. In one T-ALL patient, del(11)(q23) was found. Complex chromosomal rearrangements with the presence of numerical and structural aberrations either in one or in different clones were detected in 17/71 (24%) ALL patients: 12/17 (71%) B-ALL CD10+, and five (29%) T-ALL. Among 12 B-ALL CD10+ patients, one patient had two Ph"S chromosomes in two clones and the other ones t(9;22)(q34;q11), together with other nonspecific structural and numerical chromosomal aberrations; t(1;14)(p32;q11) was found in one clone of the patient with T-ALL and t(11;14)(p13;q11) in other patients with T-ALL and complex karyotype (Table 1).

Among 29 AML patients, a normal karyotype was found in 16 (55%) and an abnormal karyotype in 13 (45%) patients. Structural aberrations were observed in 7/13 (54%) patients with AML: t(15;17)(q22;q11), in two patients; and t(1;3)(p12;q13), inv(16)(p13;q22), inv(7)(p22;q22), del(2)(q33), and del(9)(q22) in one patient each. Among 6/13 (46%) AML patients with complex chromosomal rearrangements, t(15;17)(q22;q11) was found in two clones of one patient and t(8;21)(q22;q22) in one clone of the other patients (Table 1), together with other uncommon chromosome anomalies.

DISCUSSION

In the present study we have analyzed the immunophenotype of 239 patients and cytogenetic features of 228 patients with childhood AL referred to a single institution in Serbia and Montenegro. Our series allowed us to draw conclusions about the distribution of childhood AL in the entire country, as 60-70% of childhood acute leukemia cases from all regions were treated in this clinic.

The majority of cases (71%) were precursor B-ALL (either CD10+ or CD10-). The age distribution showed a clear peak between the ages of 2 and 4 with a predominance of precursor B-ALL CD10+. The results on age and sex distribution and phenotypic pattern of our patients were in agreement with those reported by other authors for Caucasian children (Parkin *et al.* 1998; Greaves *et al.* 1993). However, some differences were observed. First, the precursor B-ALL CD10+ displays a peak of age distribution at the age of 7, which does not fully correspond to the data from either developed or undeveloped countries. It is well documented in previous studies that earlier in the 20th century in developed countries there was an earlier appearance of the 2-5 year peak of ALL, as there was some positive association between socio-economic status and ALL incidence (Erber and Mason, 1985). The typical 2-5 year peak is evident in Serbia and Montenegro, but there is a higher frequency of patients of age 5-10 and ≥10 than was observed in developed countries (Malta *et al.* 1997). Secondly, our results indicate that the proportion of T-ALL (18%) is between the groups of countries with low and moderate proportion of T-ALL (Papamichail *et al.* 1985; Taskov *et al.* 1995; Russo 1985). We could not ascertain it fully, but our assumption is that our findings could be explained by influence of environmental factors: socio-economic development and concomitant exposure to potential leukemogenic agents (Greaves *et al.* 1993; Ramot and Magrath, 1982). The socio-economic circumstances in the region (West Balkans) are important for the proper interpretation of this study's results. This region has always been relatively underdeveloped by European standards, but the socio-

Table 2. Cytogenetic findings in 193 children with AL from Serbia and Montenegro

Immunological type	Cytogenetic analyses Total N°	Normal karyotype Total N°	Aberrant karyotype			
			Total N°	Numerical aberrations	Structural aberrations	Complex rearrangements
ALL	164	93 (57%)	71 (43%)	36	18	17
B-ALL CD10+	109	57	52	33	7	12
B-ALL CD10-	23	10	13	3	10	/
T-ALL	32	26	6	/	1	5
AML	29	16 (55%)	13 (45%)	/	7	6
AL (ALL + AML)	193	109 (56%)	84 (44%)	36	25	23

economic situation dramatically deteriorated from the beginning of the 1990s and the outbreak of the wars for the Yugoslav succession. The already grave humanitarian situation was additionaly complicated by significant demographic changes: Serbia was flooded by almost one million refugees from Serbian-populated regions of Croatia and Bosnia and Herzegovina and internally displaced persons from Kosovo and Metohija. An additional factor that remains to be carefully monitored and researched is the potential influence of toxic substances the population was exposed to during the war devastations (e.g., depleted uranium and spills from bombed-out chemical industrial facilities and oil refineries). We plan to collect detailed epidemiological data and characterize time trends in the age- and sex-specific incidence of childhood AL in the future. Such epidemiological studies have already been done in developed countries (Hjalgrim *et al*. 2003).

Cytogenetic abnormalities, both lymphoblastic and myeloid, are common in patients with AL, and some of these have prognostic significance. The most frequent translocations in ALL are: t(1;19), t(4;11), others involving the 11q23 breakpoint, and t(9;22) in B-ALL; t(8;14), t(2;8), and t(8;22) in ALL with L3 morphology; and t(11;14) and (1;14) in T-ALL. In the group of 35/164 ALL with structural (18 cases) and complex (17 cases) chromosomal rearrangments, common translocations were found in nine cases: 7 B-ALL [t(9:22) in five cases; t(8;14) in one case; t(4;11) in one case] and 2 T-ALL [t(1;14) in one case and t(11;14) in one case]. In the remaining 26 ALL patients, non-specific structural aberrations (translocations, inversions, deletions, and duplications) involving chromosomes 1, 9, 3, 19, and 18, were found. Some of the common translocations described above are recognized as predictive of outcome: t(9;22) is present in approximately 3%-4% of pediatric ALL patients having an unfavorable prognosis, which is in line with our results describing five cases of t(9;22) in the group of 164 ALL patients (3%) (Hann *et al.* 2001; Arico *et al*. 2000; Schrappe *et al*. 1998; Ribeiro *et al*. 1997); t(4;11) and others involving 11q23 occur in approximately 4% of cases, which usually show a poor response to initial therapy (Rubnitz and Pui, 1987; Rubnitz and Look, 1998). In the analyzed group of 164 ALL, these translocations were found in 2/164 ALL cases, both having B-ALL phenotype (1%). Hyperdiploidy (>50 chromosomes per cell or DNA index>1.16) occurs in 20% to 25% of cases of B-precursor ALL, but very rarely in cases of T-cell ALL (Pui and Evans, 1998) and is associated with a favorable prognosis. In our group of 164 ALL patients, hyperdiploidy (47-57 chromosomes) was found in 26/164 cases (16%) both B cell lineage ALL. In eight cases of B-ALL near triploidy (58-80 chromosomes) was found and in 2 other cases of B-ALL near tetraploidy (92± chromosomes) was observed.

The most frequent cytogenetic abnormalities in childhood AML are: t(8;21), t(15;17), and inv(16); monosomy 5/5q, 7/7q, and 17p abnormalities are classified as unfavorable. In the group of 13/29 AML patients with structural (seven cases) and complex (six cases) chromosomal rearrangements, common chromosomal abnormalities were observed in six cases: t(15;17) in three cases, and t(8;21) and inv(16) in one patient each. In the remaining seven AML patients, non-specific chromosomal rearrangements (tranlocations, inversions, deletions, and complex rearrangements) involving chromosomes 1, 3, 7, and 9 were observed. Some of the common chromosomal abnormalities in AML have prognostic significance: translocations (8;21) (Hann *et al*. 2001; Schrappe *et al*. 1998) and inv(16) account for 5%-12%, 5%-8%, and 10%-12% of AML cases and are associated with good prognosis and favorable response to therapy (Brunning *et al.* 2001; Byrd *et al.* 2002; Bloomfield *et al.* 2002; Mrozek *et al.* 1997; Marlton *et al*. 1995). In this series of 29 AML patients, these chromosomal aberrations were found in 3% (t 8/21), 10% (t 15/17), and 3% (inv16) of the cases. The difference in proportion of common chromosomal aberrations in our series, may be attributable to the small number of AML patients evaluated for cytogenetics.

We started flow cytometric immunophenotyping of childhood AL in 2002. Today, we have a well documented diagnostics for the entire nation (until November 2002 about 10-20% of the population was not covered). We expect to have complete national data for imunophenotype and cytogenetic features of childhood AL in the near future.

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У Институту за здравствену заштиту мајке и детета Србије, у периоду од октобра 1996. године до маја 2002. године, дијагноза акутне леукемије (AL) постављена је код 239 болесника. Циљ овог рада је утврђивање распрострањености имуно-фенотипских и цитогенетских особина ALкод деце из Србије и Црне Горе. На основу анализе 4 фенотипских маркера утврђена је распрострањеност имунолошких подтипова ове болести. Дијагноза акутне лимфобластне B леукемије (ALL-B) потврђена је код 169 (70.7%) болесника (137 CD19 позитивни, CD10 негативни и 32 CD19 позитивни, CD10 негативни), затим ALL-T (cyCD3 позитиван) код 37 (15.5%) болесника и AML (CD13 позитивни и/или CD33 позитивни уз истовремено одсуство антигена карактеристичних за лимфоидну ћелијску лозу) код 33 (13.8%). Однос дечака према девојчицама био је 1.5:1. Већина болесника била је узраста од 2 до 4 године и припадала је ALL-B подтипу леукемије. Други, нешто нижи врх учесталости ALL-B забележен је у узрасту од 7 година. Учесталост ALL-T од 18% (од укупног броја ALL) је слична учесталости у медитеранским земљама: Француској (19.4%), Грчкој (28.1%), јужној Италији (28.3%) и Бугарској (28%). Цито-генетичке анализе извршене су код 193 болесника: 164 ALL и 29 AML. Нормалан кариотип доказан је код 57% ALL и 55% AML. Цитогенетске аберације, укључујући и нумеричке, структурне и комплексне, откривене су код 43% оболелих од ALL и 45% оболелих од AML. Наши резултати представљају допринос епидемиолошким аспектима проучавања акутних леукемија код деце.