CLINICAL AND GENEALOGICAL RESEARCH IN FAMILIES WITH CHILDREN SUFFERING FROM ACUTE LEUKEMIA

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S u m m a r y. In order to establish genetic nature of predisposition to acute leukemia in children clinical and genealogical research was conducted in 209 families with the history of acute leukemia in children compared to 192 families with healthy children of corresponding age and sex. Conspicuous is increased susceptibility to malignant tumors in III degree relatives of leukemia children (the risk is doubled), whereas maternal tumor inheritance triples oncological risk. Families with leukemia children have 8 times higher risk for intestinal cancer, whereas other malignances, e.g. solid tumors or blood tumors were not found. The results partly comply with the data of other researchers, and partially indicate probable genetic involvement among the Ukrainian population, with characteristic features of malignant tumor formation.
K e y w o r d s: acute leukemia, children, clinical research, genealogical research.

INTRODUCTION

Modern clinical medicine cannot go without genetic methods. When doctor consults the family of a child with malignant tumor, they should first of all identify whether the tumor is sporadic or inherited. Therefore, treatment efficacy and prognosis should consider similar cases in the patient's family history [7, 23].

Development of malignant tumors in children suggests genetic incapability of the body to destroy cells with abnormal genome already in the prime of life. The occurrence of the most widespread sporadic tumors is implicitly influenced by the external provocative factors initiating pathological process, and that is based on the presence of multiple mutant alleles in genome with additional carcinogenic effect [5, 20]. The susceptibility to hereditary oncological diseases is determined by genetic structure of populations clearly manifested when patients remain in certain isolation (geographical, ethnic, religious), when the probability of related marriages rises [1, 8, 21, 22].

In order to establish genetic nature of any disease (monogenic, hereditary or polygenic, multifactorial), clinical and molecular genetic markers are used, but clinical and genealogical research of the family remains to be the basic one, which is simple-to-use and in terms of economy is a low cost procedure [4, 13]. The essence of genealogical method lies in establishment of related ties and tracing the signs or disease among close or distant, direct or indirect relatives. The purpose of study was to investigate the extent of malignant tumors that run in families with high risk for oncological pathology in children.

MATERIALS AND METHODS

Clinical and genealogical research was conducted in 209 proband's families, aged 3 months to 18 years with an oncohematological pathology (127 boys and 82 girls with acute leukemia), treated at Hematology Department of Western-Regional Specialized Children's Center (Lviv). The control group consisted of 192 families with healthy children of corresponding age and sex. The examined families reside on the territory of Lviv district (Ukraine).

The largest proportion of patients had acute lymphoblastic leukemia (ALL – 180 patients, 86.1%), the smallest group were the patients with acute myeloid leukemia (AML – 29 patients,

13.9%); 98 patients live in the country (46,9%), and 111 patients (53.1%) were city residents.

RESULTS AND DISCUSSION

The age of patients ranged from 3 months to 17 years, (median 4.1±0.9 years), and the controls were 2 to 18 years old (median 4.6±0.8 years). The majority of children with an oncohematological pathology were at the age of 5–9 years –78 patients (37.8%). The smallest group were children under 1 year – 6 patients (2.9%). The youngest patient was 3 months, and died soon. Almost all patients under one year were diagnosed with acute lymphoblastic leukemia (single case of AML). Most patients, 149 (71.3%) had grade II–III cancer.

In the group of 209 pediatric patients there were 120 (57.4%) families with acute leukemia, or malignant tumors: in 103 families there was history of ALL and 17 – AML. In the control group malignant tumors were diagnosed in 103 out of 192 families (53.6%). Overall frequency of oncologic diseases in families from the examined and control group was not significantly different, i.e. 57.4% and 53.6% respectively (χ^2=0.58, p>0.05).

Clinical and genealogical research, and the review of data on disease incidence in I-III degree relatives revealed 4,780 family members in the examined group and 4,463 family members in the control group had cancer (Table 1). In the examined group there were no cases of oncologic pathology among 681 I degree relatives, whereas in the control group (645 relatives) there were two cases; the difference between groups is insignificant (χ^2=0.46, p>0.05). In the families of patients increased frequency of malignant tumors was observed among III degree relatives (127 out of 2,663), as opposed to the control group (60 out of 2,294): 4.8% and 2.6%, respectively (χ^2=15.7, p<0.001). The risk of oncological pathology among III degree relatives was almost twice higher (OR=1.86 [95% CI: 1.36–2.55]).

On the other hand, in the control group oncological diseases were detected in II degree relatives: 6.3% (96 cases among 1524 relatives) against 4.4% (63 persons among 1436 relatives) in the group of examined patients (χ^2=5.32, p=0.02) (Table 1).

Among II degree relatives in the examined group malignant tumors were frequent in paternal grandmothers: 6.7% against 2.1% in the controls (χ^2=4.97, p=0.03). At the same time, in the control group the frequency of disease in maternal aunts was significantly higher (7.2% against 1.6% in the examined group, χ^2=7.43, p<0.01), maternal uncles (6.9% and 1.5% respectively, χ^2=4.88, p<0.05), and also paternal uncles (6.6% and 2.0% respectively, χ^2=3.99, p<0.05).

Malignant tumors burden in maternal relatives was higher in the control group among II degree relatives (7.5% against 4.9% in the examined group, χ^2=4.11, p<0.05), whereas in the III degree relatives the burden was significantly higher in the families of the pediatric patients with AL (4.8% and 1.6% in the controls, χ^2=25.86, p<0.001). In the last case, the difference turned out to be so significant that it showed thrice increase in the risk for a malignant tumor in adult relatives of pediatric patients, in III degree relatives on maternal side (OR=3.16 [95% CI: 1.98–5.03]).

The spectrum of oncological diseases in the families of pediatric patients with leukemia (4,780 relatives) included gastric cancer – 37 (0.8%), lung cancer – 25 (0.5%), abdominal cancer – 22 (0.5%), gynecological cancer –17 (0.4%), breast cancer –16 (0.4%), leukemia – 15 (0.3%), intestinal cancer – 9 (0.2%), and only in individual cases – osseal lymphoma and sarcoma (Table 2). In the control group (4,463 relatives) the most frequent were breast cancer – 28 (0.6% families), lung cancer – 23 (0.5%), abdominal cancer – 23 (0.5%), visceral cancer – 18 (0.4%), gynecological cancer – 13 (0.3%), and only in individual cases – bladder cancer, osseal lymphoma and sarcoma.

Table 1. Frequency of malignant tumors among I-III degree relatives in pediatric patients with acute leukemia and in control group.

Degree of relation	Relatives of patients with acute leukemia (n=4,780)		Relatives of control group members (n=4,463)		Statistical indices				
	n	%	n	%	χ^2	P	OR 95%CI	Lower limit	Upper limit
I	0	0	2	0.3	0.56	0.46	0.19	0.01	3.94
II	63	4.4	96	6.3	5.32	0.02*	0.68	0.49	0.95
III	127	4.8	60	2.6	15.7	<0.001*	1.86	1.36	2.55
Total	190	4.0	158	3.5	1.2	0.27	1.13	0.91	1.4

* significant differences (p<0.05)

T a b l e 2. Spectrum of malignant tumors among relatives in pediatric patients with acute leukemia and in the control group

Cancer	Relatives of patients with acute leukemia (n=4,780)		Relatives of control group members (n=4,463)		Statistical indices				
	n	%	n	%	χ^2	P	OR 95%CI	Lower limit	Upper limit
gastric	37	0.8	23	0.5	2.395	0.122	1.506	0.893	2.538
breast	16	0.3	28	0.6	4.172	0.041*	0.532	0.287	0.985
lung	25	0.5	23	0.5	0.003	0.959	1.015	0.575	1.791
abdominal	22	0.5	18	0.4	0.174	0.677	1.142	0.612	2.132
gyneco-logical	17	0.4	13	0.3	0.296	0.587	1.222	0.593	2.518
intestinal	9	0.2	1	0.02	4.442	0.035*	8.417	1.066	66.466
leukemia	15	0.3	6	0.1	3.276	0.07	2.338	0.906	6.032
lymphoma	2	0.04	2	0.05	0.186	0.666	0.934	0.131	6.631

* significant differences ($p<0.05$)

The frequency and spectrum of detected malignant tumors did not differ in families from the examined and control groups ($p>0.05$), except in cases of breast cancer and intestinal cancer. Breast cancer occurred with significantly higher frequency in the control group members compared to the families with leukemia, 0.6% vs. 0.3% ($\chi^2=4.17$, $p<0.05$). Thus breast cancer, rather frequent in general population, turned out to be considerably less widespread in the families with a child suffering from AL. Conversely, in the families with cases of leukemia diagnosed at an early age, a considerable number of intestinal cancer was observed: 0.2% against 0.02% in the control group ($\chi^2=4.44$, $p<0.05$). In the examined group, intestinal cancer was diagnosed only in female relatives, in the control group a great- grandfather was the only cancer patient. The exposure to intestinal cancers in the families burdened with AL in children turned out to be 8 times higher than in general population (OR=8.42 [95% CI: 1.07–66.47]).

Notwithstanding is the fact that in the examined group of the families of children with leukemia, the frequency of oncohematological diseases was not different at 95% probability (0.3% vs. 0.1% in the control; $\chi^2=3.28$, $0.05<p=0.07$), even though it was sufficiently close to critical values.

The frequency of oncological disease in the families with leukemia children was not significantly different from the population indices. This complies with other data [25], which found no relation between family cancer history and leukemia occurrence in early years across the population of the USA. The spectrum of malignant tumors in the families for higher oncological risk complies with research data [11] on the increased percent of disease across the Ukrainian population. Our results found increased relative risk of breast cancer and intestinal cancer development in proband families with acute leukemia, the finding which complies with the other data [16], but they contradict the statement of the increased risk for other cancer types formation [16, 18]. In general, modern literature presents the burdening degree of proband family tree with leukemia with cases of malignant tumors, including oncohematological types [6, 12, 14, 18]. Some authors consider family cancer history to be a risk factor for acute leukemia occurrence in children, especially in conditions of family history with leukemia and lymphoma [6,14,18]. Others oppose to it [26], e.g. Hemminki K. et al. [9] emphasize that family risks of cancer occurrence are important to genetic counseling and understanding of malignant tumor etiology.

According to the data of Swedish Family-Cancer Database, covering data of 10.2 million people, family risk for posterity increases considerably, when cancer occurred in the family of a I degree relative [2]. Kharazmi E. et al. [10], compared the frequency of acute leukemia in children from Sweden and Finland (3,994 people), and found a high risk of that pathology development for twins and siblings. Increased risk of leukemia occurrence was found in probands, whose siblings were diagnosed with such pathology in comparison with those who had parents affected [26]. The Ukrainian patients did not significantly differ in the frequency of malignant tumors among I degree relatives of children with leukemia and the finding complies with other data [15, 19, 24], that malignant blood tumors in parents did not significantly affect the disease occurrence in children.

The families of the Ukrainian acute leukemia patients were found to have significantly increased frequency of intestinal cancer, the risk of occurrence was increased by 8.4 times. This complies with other findings [3] that significantly more relatives with leukemia were noted among probands

with intestinal cancer. According to the literature data [18] families with intestinal cancer patients have 1.5 times higher risk for acute lymphoblastic leukemia in their relatives, and the risk for acute myeloblastic leukemia is 3.9 times higher.

Gastric cancer turned out to be the most widespread oncological pathology in the families with the history of acute leukemia in children. However, a reliable difference from controls failed to be proved under 95% probability (χ^2=2.39, p>0.05). In addition, other researchers [18] highlighted the fact that gastric cancer among proband relatives with leukemia was 1.8 times more frequent than in the controls, and others [15] found that frequency of gastric cancer doubled among proband parents with chronic lymphocytic leukemia.

Our research found a significantly lower incidence of breast cancer in the families of children with leukemia compared to the controls (0.3% and 0.6% respecively, χ^2=4.17, p<0.05). This is not consistent with other conclusions [17] that breast cancer may be considered one of leukemia liability markers, but it is consistent with other findings [18] suggesting no difference in breast cancer frequency in the families of children with leukemia compared with the controls. According to data [15] breast cancer frequency is increased among mothers and sisters of a proband with chronic lymphocytic leukemia.

CONCLUSIONS

Based on the results of the research conducted, clinical and genealogical analysis may considerably improve calculation of risk occurrence of oncological pathology in the families with children diagnosed with acute leukemia. Conspicuous is increased susceptibility to malignant tumors in III degree relatives of leukemia child (the risk is doubled), whereas maternal tumor inheritance triples oncological risk. Families with leukemia children have 8 times higher risk of intestinal cancer, however no correlation with other malignant, solid tumors and blood tumors was found. The results partly comply with the data of other researchers, and partially indicate probable properties of genetic structure of the Ukrainian population, affecting characteristic features of malignant tumor formation.

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