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IMMUNOGENETIC STATUS OF CHILDREN WITH MILD IODINE DEFICIENCY, LATENT IRON DEFICIENCY AND THEIR COMBINATION

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Abstract. Due to the prevalence of microelementosis (including iodine and iron deficiencies), cytogenetic abnormalities in children with microelement imbalance were studied.

The objective of the research was to assess the abnormalities in the immunogenetic status of the organism by the frequency and spectrum of chromosomal aberrations, associations of acrocentric chromosomes and to determine the frequency of micronuclei in peripheral blood leukocytes in children with mild iodine deficiency, latent iron deficiency and their combination.

Materials and methods. There were examined 68 boys and 65 girls at the age of 6 to 18 years. In the analysis of indicators, the main attention was paid to the age- (6-11 and 12-18 years) and gender-related peculiarities.

Results and discussion. In all the children, associations of acrocentric chromosomes of two chromosomes were most commonly observed: in the control group, this indicator was 73.74%; in iodine deficiency, it was 67.72%; in iron deficiency, it was 67.68%; in combined microelementosis, the indictor was 68.68%. Chromosomal abnormalities were recorded in 56.03% of children. However, in the control group, this indicator was 40.94%, while in microelement imbalance, it was 71.13%. The most significant changes in the spectrum of chromosomal aberrations were identified in iodine and iron deficiencies (increase in the frequency of paired fragments, dicentrics, translocations, and the presence of a ring chromosome).

Conclusions. Changes in the frequency and characteristics of the number of chromosomes in associations of acrocentric chromosomes, the frequency and spectrum of chromosomal aberrations, and the number of micronuclei indicated genotype instability, especially in iodine deficiency and combined microelement imbalance.

Keywords: mild iodine deficiency; latent iodine deficiency; chromosomal aberrations; association of acrocentric chromosomes; children of school age.

Problem statement and analysis of the recent research

An important indicator of the immunogenetic status of the organism is the state of the chromosomal apparatus: the level of chromosomal abnormalities, associative ability of acrocentric chromosomes. One of the methods for studying the effects of various exo- and endogenous factors on human immunoreactivity is the cytogenetic analysis of peripheral blood lymphocytes (PBL), which reflects the specific reaction of the immune cells to any antigenic stimulus. The cytogenetic analysis of the PBL is an internationally recognized method for assessing the immunogenic status of the organism. Numerous studies of the chromosomal apparatus being known today are devoted to the study of associations of acrocentric chromosomes (AAC) [2, 20], the frequency and spectrum of chromosomal aberrations (CA) [1, 5, 7, 9, 11, 17, 21], micronuclei (MN) analysis [8] in children and adults in various diseases. 5 pairs of acrocentric chromosomes of groups D [13, 14, 15] and G [21, 22] in the short arms of which the clusters of ribosomal genes are localized thereby providing the formation of the protein synthesis apparatus, have the ability to associate. The adaptive response of cells depends on the ability of the latter one. Several works provided the results of a combined study of the association capacity of chromosomes and the frequency of CA [20]. However, there are no data on cytogenetic abnormalities in children with microelement imbalance, iodine deficiency and iron deficiency in particular.

The objective of the research was to assess the abnormalities in the immunogenetic status of the organism by the frequency and spectrum of CA, AAC and to determine the frequency of MN in PBL in children with mild iodine deficiency, latent iron deficiency and their combination.

Materials and methods

133 apparently healthy children (68 boys and 65 girls) at the age of 6-18 years were examined. All schoolchildren were divided into four groups: Group I included boys and girls with appropriate iodine and iron supply (the control group); Group II comprised children with low iodine supply without iron deficiency; Group III included pupils with latent iron deficiency and adequate iodine supply; Group IV comprised children with mild iodine deficiency and latent iron deficiency.

The level of iodine supply was estimated based on daily urinary iodine excretion [12, 25]. The state of iron supply to the body was evaluated by the level of hemoglobin (Hb) in the capillary blood, serum iron (SI), total iron-binding capacity (TIBC), serum ferritin (SF) [13, 15]. The cytogenetic study was performed according to the standard scheme: cultivating the PBL, preparing and analyzing the preparations of metaphase chromosomes (in accordance with the methodological recommendations of the Ministry of Health of Ukraine (2003) [14]. There were studied AAC [2, 6], frequency and spectrum of CA [1, 6, 9]. MN analysis [8] was carried out.

The studies were performed in the consecutive representative groups. Statistical analysis of data was carried out using the statistical software package StatisticSoft 7.0. The difference was considered statistically significant at $p<0.05$.

Results and discussion

During the analysis of the absolute frequency of AAC, there were no significant changes between children of the experimental subgroups and the control group. However, there was a steady tendency toward the increase in the frequency of AAC in children with iodine deficiency (22.17%), iron deficiency (23.09%) and combined microelementosis (21.65%). In particular, in mild iodine deficiency, the frequency of AAC in children (mostly in girls) decreased by 20.85% with age. In boys, the increase in AAC by 33.58% was detected (Table 1). Latent iron deficiency led to the reduction in the metaphases with AAC by 18.05% in older children as compared to younger ones (mainly in girls, by 36.57%).

The same tendency was observed in combined microelement deficiency; in particular, the frequency of AAC in girls was 26.53% lower, and in boys, it was 30.82% higher.

For the analysis of the nucleolus-forming ability of chromosomes, the frequency of AAC with different numbers of acrocentrics in one association was analyzed.

Table 1. Frequency of associations of acrocentric chromosomes (%) in children, (M±m)

Groups of children, gender	Frequency of associations of acrocentric chromosomes, %			
	Group I (the control group)	Group II (mild iodine deficiency)	Group III (latent iron deficiency)	Group IV (mild iodine deficiency and latent iron deficiency)
6-11 years, n=68	25.20±5.72	24.75±5.57	25.38±4.96	21.89 ±5.67
Girls, n=33	26.25±6.42	29.40±6.12	27.29±6.79	25.18±7.85
Boys, n=35	24.16±5.01	20.10±5.02	23.48± 3.41	18.59±3.48
12-18 years, n=65	17.10±4.65	19.59±4.65	20.80±2.41	21.41± 5.96
Girls, n=32	16.98±3.86	12.32±3.86	17.31±3.69	18.50± 4.13
Boys, n=33	17.21±5.44	26.85±5.44	24.28±1.13	24.32± 7.78

In all the children AAC of two chromosomes were most commonly observed: in the control group, this indicator was 73.74%; in iodine deficiency, it was 67.72%; in iron deficiency, it was 67.68%; in combined microelementosis, the indictor was 68.68%. However, the number of AAC of four chromosomes increased (the most significantly in combined iodine and iron deficiencies – 5.86%, whereas in the control group – 2.72%). It is necessary to emphasize that in children with latent iron deficiency and combined microelementosis, an increase in the frequency of AAC of three chromosomes, 28.07% and 27.06% respectively, as compared to the control group (23.54%) was detected (Fig. 1).

The study of the distribution of AAC by the number of associated acrocentrics in one association per 100 metaphases revealed that in younger boys with mild iodine deficiency, the number of AAC of three chromosomes increased by 2.23 times ($p_{1-2}<0.05$) and the number of AAC of four chromosomes increased by 81.13 % ($p_{1-2}<0.05$) as compared to the control group (Table 2). In girls, these indicators had a slight tendency to elevate, but they were not reliable.

In boys with latent iron deficiency at the age of 6-11 years, the number of AAC of three chromosomes significantly increased by 2.88 times ($p_{1-3}<0.01$) and the number of AAC of four chromosomes increased by 66.03% ($p_{1-3}<0.05$) as compared to the control group. In girls of the same age, there was observed the decrease in the number of AAC of four chromosomes by 41.08% ($p_{1-3}<0.05$) as compared to the control group and by 56.57% ($p_{2-3}<0.05$) as compared to those with mild iodine deficiency.

In boys with combined microelementosis at the age of 6-11 years, the number of associations of three chromosomes decreased by 53.47% ($p_{2-4}<0.05$) and the number of associations of four chromosomes decreased by 64.93% ($p_{2-4}<0.01$) as compared to those with mild iodine deficiency. In girls, the number of AAC of four acrocentrics increased by 89.91% ($p_{3-4}<0.01$).

In older pupils, changes in the number of chromosomes in one association differed from those in younger ones. The distribution of AAC by the number of associated acrocentrics in one association in children at the age of 12-18 years is presented in Table 3.

The greatest sensitivity of the chromosomal apparatus was detected in older children with mild iodine deficiency and latent iron deficiency. Thus, the number of associations of three chromosomes significantly prevailed in girls with latent iron deficiency - by 2.36 times ($p_{3-4}<0.05$). There was observed the increase in the frequency of AAC of four chromosomes in boys by 3.69 times ($p_{1-4}<0.001$) and in girls by 77.45% ($p_{1-4}<0.05$) as compared to the control group. The frequency of AAC of four chromosomes increased by 3.86 times ($p_{2-4}<0.001$) in boys and by 92.56% in girls ($p_{2-4}<0.05$) as compared to those with mild iodine deficiency and by 3.12 times ($p_{3-4}<0.01$) in both boys and girls as compared to those with latent iron deficiency.

In all examined children, in general, the karyotype corresponded to 46,XX or 46,XY. Chromosomal abnormalities were recorded in 56.03% of children. However, in the control group, this indicator was 40.94%, while in microelement imbalance, it was 71.13%, i.e. it increased by 1.74 times. The study of the control group showed that with age changes in the structure of chromosomes were more likely

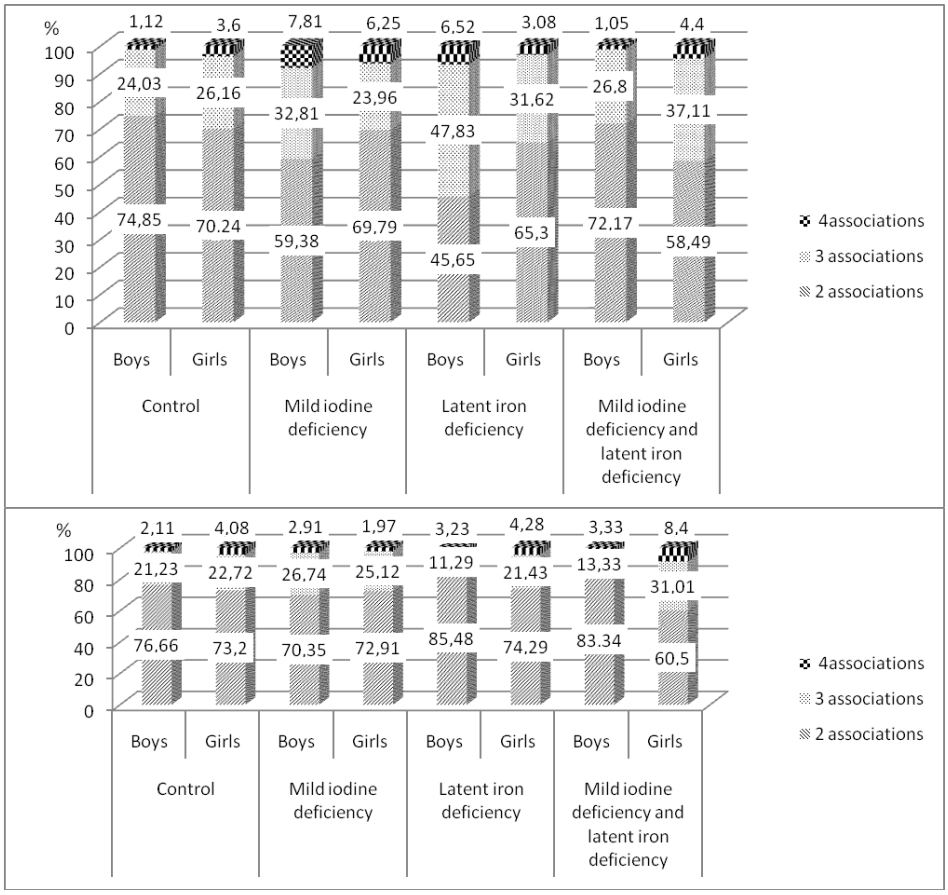

Fig. 1. Histogram of associations of acrocentrics (%) by the number of chromosomes in one association in children at the age of 6-11 (à) and 12-18 years (b) in microelementosis and in the control group

Table 2. Distribution of associations of acrocentric chromosomes by the number of associated acrocentrics in one association in children at the age of 6-11 years, (M±m)

Number of chromosomes in one association	Group I (the control group)		Group II (mild iodine deficiency)		Group III (latent iron deficiency)		Group IV (mild iodine deficiency and latent iron deficiency)	
	Boys (n=8)	Girls (n=8)	Boys (n=9)	Girls (n=9)	Boys (n=8)	Girls (n=8)	Boys (n=10)	Girls (n=8)
2	18.69±4.01	15.07±2.16	8.58±2.12	17.23±2.29	9.65±1.79	18.09±2.74	13.56±2.2	13.21±2.21
3	3.88±0.71	9.32±1.91	8.64±1.48 $p_{I-2}<0.05$	9.66±2.18	11.19±1.8 $p_{I-3}<0.01$	8.10±2.03	4.02±1.0 $p_{2-4}<0.05$ $p_{3-4}<0.01$	9.9±1.91
4	1.59±0.25	1.85±0.18	2.88±0.41 $p_{I-2}<0.05$	2.51±0.56	2.64±0.32 $p_{I-3}<0.05$	1.09±0.19 $p_{I-3}<0.05$ $p_{2-3}<0.05$	1.01±0.21 $p_{2-4}<0.01$ $p_{3-4}<0.01$	2.07±0.24 $p_{3-4}<0.05$

Note: p with Arabic numerals – the comparison between subgroups

Table 3. Distribution of associations of acrocentric chromosomes by the number of associated acrocentrics in one association in children at the age of 12-18 years, (M±m)

Number of chromosomes in one association	Group I (the control group)		Group II (mild iodine deficiency)		Group III (latent iron deficiency)		Group IV (mild iodine deficiency and latent iron deficiency)	
	Boys (n=9)	Girls (n=8)	Boys (n=8)	Girls (n=8)	Boys (n=8)	Girls (n=8)	Boys (n=8)	Girls (n=8)
2	10.22±1.34	11.48±2.81	20.59±3.8 $p_{I-2}<0.05$	7.24±1.60	18.09±2.79 $p_{1-3}<0.05$	14.28±2.78 $p2_{I-3}<0.05$	13.16±2.46	10.55±2.32
3	6.27±1.39	4.48±1.67	5.57±1.62	4.14±1.44	5.34±1.32	2.6±0.73	8.5±0.89	6.14±1.35 $p_{3-4}<0.05$
4	0.72±0.09	1.02±0.11	0.69±0.11	0.94±0.20	0.85±0.20	0.58±0.12 $p_{I-3}<0.01$	2.66±0.30 $p_{I-4}<0.001$ $p_{2-4}<0.001$ $p_{3-4}<0.01$	1.81±0.30 $p_{I-4}<0.05$ $p_{2-4}<0.05$ $p_{3-4}<0.01$

Note: p with Arabic numerals – the comparison between subgroups

to occur, although the general index of CA frequency in the control group varied insignificantly (Table 4). There was a subtle tendency toward its increase in children at the age of 12-18 years in comparison with the corresponding indicators in the first age group.

The analysis of CA frequency found that combined microelement imbalance had a more significant effect on girls than boys as indicated by higher frequency of CA (by 4.93% and 6.50% in Group I and Group II, respectively). With age, in combined microelement imbalance, the number of chromosomal abnormalities tended to increase regardless of gender (by 15.98% in girls and by 15.19% in boys).

In girls of the first group with combined microelement imbalance, the number of chromosomal abnormalities increased by 1.61 times ($p_{2-4}<0.05$) as compared to that in iodine deficiency. In all children of the second group, the frequency of CA increased significantly as compared to that in iodine and iron deficiencies - by 1.47 and 1.82 times, respectively ($p_{2-4}<0.05$). Among older children, boys were found to be more sensitive to microelement deficiency. In particular, there was an increase in the frequency of CA by 1.58 times ($p_{3-4}<0.05$) in comparison with the indicator in iodine deficiency and by 1.86 times ($p_{3-4}<0.05$) in comparison with the indicator in iron deficiency. In this age group of girls, a significantly higher incidence of the abnormalities in chromosomal structure was detected as compared to iron deficiency - by 1.79 times ($p_{3-4}<0.05$).

A natural continuation of our work was the study of the spectrum of CA. In all children of the control group, chromatid aberrations were dominant: ruptures, gaps, single fragments (49.90%, 31.12% and 18.9%, respectively). Age-related and gender peculiarities were as follows: in boys at the age of 6-11 years, three types of CA, namely ruptures, gaps (45.08%) and single fragments (9.84%) were mainly found, while in girls, the latter ones were absent. Among older pupils, in girls, there were found ruptures, gaps and single fragments (33.33%, respectively), whereas in boys, there were no gaps (Fig. 2).

A detailed analysis of CA spectrum in children at the age of 6-11 years with mild iodine deficiency proved the predominance

Table 4. Frequency of chromosomal aberrations in children of different age, (M±m)

Age of children, years	Frequency of chromosomal aberrations %			
	Group I (the control group)	Group II (mild iodine deficiency)	Group III (latent iron deficiency)	Group IV (mild iodine deficiency and latent iron deficiency)
6-11 years, n=68	1.91±0.43	3.63±0.21 $p_{I-2}<0.01$	3.58±0.57 $p_{I-3}<0.05$	5.20±0.79 $p_{I-4}<0.01$
Girls, n=33	1.89±0.29	3.30±0.24 $p_{I-2}<0.01$	3.85 ±0.36 $p_{I-3}<0.01$	5.32±0.72 $p_{I-4}<0.01$ $p_{2-4}<0.05$
Boys, n=35	1.93±0.57	3.96±0.18 $p_{I-2}<0.01$	3.31±0.77	5.07±0.85 $p_{I-4}<0.05$
12-18 years, n=65	2.01±0.49	4.10 ±0.46 $p_{I-2}<0.05$	3.31±0.66	6.01±0.58 $p_{I-4}<0.001$ $p_{2-4}<0.05$ $p_{3-4}<0.05$
Girls, n=32	1.97±0.31	4.51±0.63 $p_{I-2}<0.01$	3.47±0.58 $p_{I-3}<0.05$	6.17±0.77 $p_{I-4}<0.001$ $p_{3-4}<0.05$
Boys, n=33	2.05±0.67	3.69±0.29	3.14±0.74	5.84±0.39 $p_{I-4}<0.01$ $p_{2-4}<0.01$ $p_{3-4}<0.05$

Note: p with Arabic numerals - a significant difference between similar indicators of different subgroups

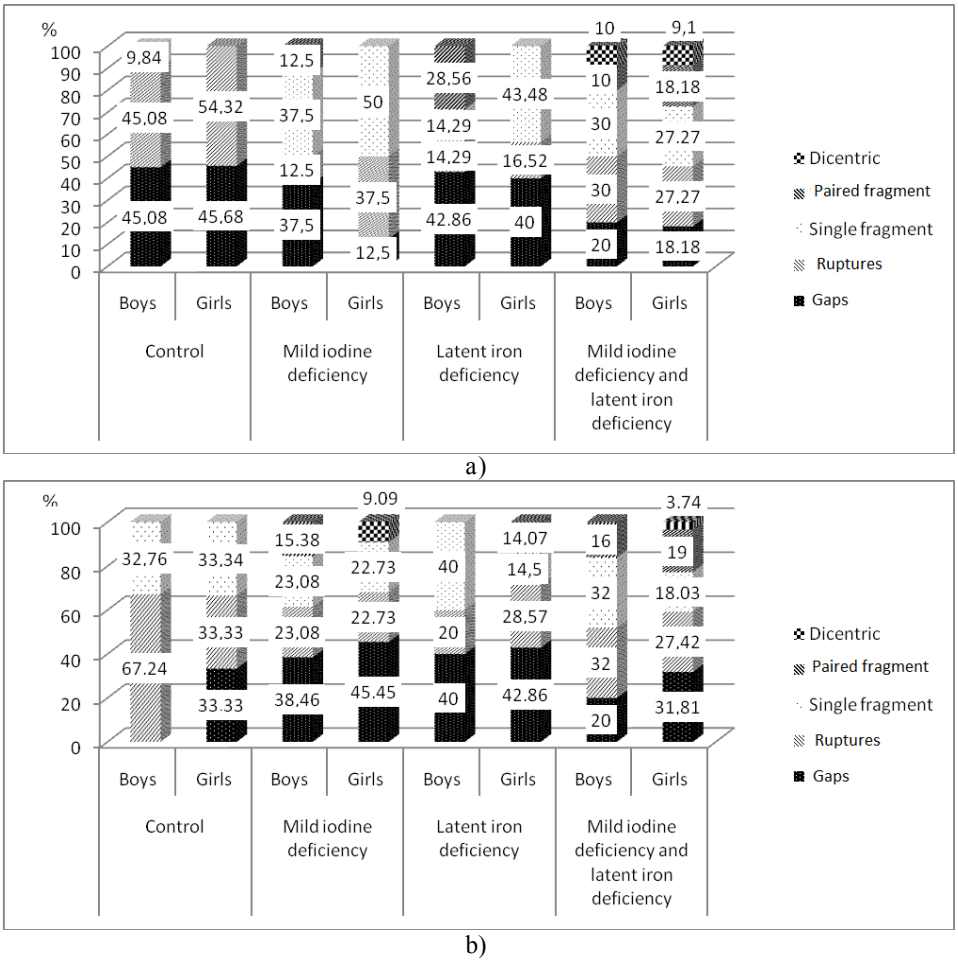

Fig. 2. Spectrum of chromosomal aberrations (%) in children (à – 6-11 years; b – 12-18 years)

of chromatic aberrations – gaps and single fragments (Table 5). In boys, there was a significant increase in the number of single fragments - by 6.47 times (p_{1-2}<0.05) and chromosomal-type CA – paired fragments (0.64±0.12) as compared to the control group, while in girls, there was found a considerable number of ruptures (37.5%) of two chromatids (Fig. 2).

In children of the first group with latent iron deficiency, chromatid aberrations prevailed as well: gaps (in girls, their number increased by 49.42% (p_{1-3}<0.01, ruptures of predominantly one chromatid). A characteristic feature of the effect of iron deficiency on the girls' organisms was a large number of single fragments (43.48% of all CA (Fig. 2). The feature of the spectrum of CA in boys with iron deficiency was the increase in the frequency of paired fragments by 12.50% as compared to that in iodine deficiency.

In the spectrum of CA in children at the age of 6-11 years with iodine and iron deficiencies, chromatid aberrations were represented by gaps, ruptures of one of chromatids (30.0% in boys and 27.27% in girls) and single fragments. In boys, the numbers of ruptures and single fragment were 82.76% (p_{1-4}<0.05) and 6.11 (p_{1-4}<0.01) times higher as compared to the control group. The number of ruptures increased by 91.56% (p_{2-4}<0.05) as compared to the data in children with mild iodine deficiency and by 96.30% (p_{3-4}<0.05) as compared to the data in children with latent iron deficiency. For the first time ever, paired fragments in girls (18.18% of all CA) were identified as characteristic chromosomal abnormalities in combined deficiencies of microelements (Fig. 2). In boys, they were detected with almost the same frequency as in iodine deficiency.

The second feature of CA spectrum was the presence of dicentrics, such as chromosomal-type CA in both boys and girls. For the first time ever, translocation of chromosome of group C was identified in one boy.

In CA spectrum of children at the age of 12-18 years with mild iodine deficiency, there were a lot of gaps in both boys and girls - 38.46% and 45.45% of all CA, respectively (Fig. 2). In boys of the control group, such CA were not identified; however, the frequency of ruptures reduced by 54.01% (p_{1-2}<0.01) as compared to the control group (Table 6). Although single fragments in both girls and boys had almost the same frequency (22.73 and 23.08%, respectively); in boys, these chromatid abnormalities prevailed the control indicators by 2.12 times (p_{1-2}<0.05).

There was proven the increase in the frequency of CA in all children with iodine deficiency, iron deficiency and combined microelementosis as compared to the control group. With age, changes in the structure of chromosomes were more likely to occur. There were determined changes in CA spectrum in children with iodine deficiency, iron deficiency and combined pathology as compared to those in healthy children. There were identified chromatic (gaps, ruptures of one of chromatids, single fragments) and chromosomal (ruptures of one of chromatids, paired fragments, dicentrics, ring chromosomes, translocations) aberrations. Gaps were found most frequently; their frequency did not depend on either age or gender. In ruptures, there was no connection between the fragment and chromosome; one of the fragments on the metaphase plate was shifted. In 67.02% of children, ruptures attributed to gaps were observed since the fragments of chromosome were not shifted.

The increase in the frequency of single fragments as chromatid abnormalities in all children and the presence of paired fragments (markers of chromosomal-type CA) only in children of two age groups were typical in iodine deficiency. In girls of the second group with iodine deficiency, there were identified single dicentric chromosomes being more typical for those affected by radiation.

The features of CA spectrum in children with iron deficiency consisted in the predominance of paired fragments in children of the first group as compared to those with iodine deficiency, and their detection in girls at the age of 12-18 years. Among chromatid aberrations, gaps ranked first in all children and single fragments - in boys of the first group and girls of the second group.

The most significant changes in CA spectrum were identified in iodine and iron deficiencies. The determinative factor was the increase in the frequency of chromosomal-type

Table 5. Spectrum of chromosomal aberrations in children at the age of 6-11 years, (M±m)

Spectrum of chromosomal aberrations	Groups							
	Group I (the control group)		Group II (mild iodine deficiency)		Group III (latent iron deficiency)		Group IV (mild iodine deficiency and latent iron deficiency)	
	Boys (n=8)	Girls (n=8)	Boys (n=9)	Girls (n=9)	Boys (n=8)	Girls (n=8)	Boys (n=10)	Girls (n=8)
Gaps	0.87±0.09	0.87±0.08	1.26±0.42	1.23±0.28	0.72±0.12	1.3±0.10 $p_{1-3}<0.01$	1.15±0.22	1.03±0.09
Ruptures	0.87±0.09	1.02±0.14	0.83±0.1	0.93±0.11	0.81±0.09	1.05±0.20	1.59±0.27 $p_{1-4}<0.05$ $p_{2-4}<0.05$ $p_{3-4}<0.05$	1.31±0.13
Single fragment	0.19±0.03		1.23±0.32 $p_{1-2}<0.05$	1.14±0.24	1.06±0.20 $p_{1-3}<0.01$	1.5±0.14	1.16±0.26 $p_{1-4}<0.01$	0.98±0.08
Paired fragments	-	-	0.64±0.12	-	0.72±0.10	-	0.60±0.09	1.03±0.09
Dicentric	-		-	-	-	-	0.6±0.09	0.97±0.08

Note: p with Arabic numerals - a significant difference between similar indicators of different subgroups

Table 6. Spectrum of chromosomal aberrations in children at the age od 12-18 years, (M±m)

Spectrum of chromo-somal aberrations	Groups							
	Group I (the control group)		Group II (mild iodine deficiency)		Group III (latent iron deficiency)		Group IV (mild iodine deficiency and latent iron deficiency)	
	Boys (n=9)	Girls (n=8)	Boys (n=8)	Girls (n=8)	Boys (n=8)	Girls (n=8)	Boys (n=8)	Girls (n=8)
Gaps	-	0.66±0.10	1.35±0.32	1.94±0.45 $p_{1-2}<0.05$	1.19±0.09*	1.53±0.30 $p_{1-4}<0.05$	1.16±0.26	1.81±0.40 $p_{1-4}<0.05$
Ruptures	1.37±0.16*	0.66±0.10	0.63±0.09 $p_{1-2}<0.01$	0.97±0.12	0.77±0.08 $p_{1-3}<0.05$	0.95±0.12	1.58±0.06 $p_{2-4}<0.001$ $p_{3-4}<0.001$	1.04±0.21
Single fragment	0.68±0.09***	0.65±0.12	1.44±0.29 $p_{1-2}<0.05$	0.88±0.13	1.18±0.10 $p_{1-3}<0.01$	0.42±0.09***	1.60±0.09 $p_{3-4}<0.001$	1.33±0.61
Pair fragments	-	-	0.27±0.04*		-	0.57±0.07	1.50±0.12*** $p_{2-4}<0.001$	1.54±0.40
Dicentric		-		0.72±0.09				0.46±0.03*** $p_{2-4}<0.05$

Notes: * - p<0.05, ** - p<0.01, *** - p<0.001 – statistically significant changes between the corresponding age groups; p with Arabic numerals - a significant difference between similar indicators of different subgroups

CA: paired fragments in all children, dicentrics in all children, except children at the age of 12-18 years; translocations in boys of the first group and girls of the second group, ring chromosome in older boys.

Conclusions

The dependence of immunocytogenetic parameters (AAC, CA and MN) on iodine deficiency, iron deficiency and their combined insufficiency in all examined children was determined. Changes in the frequency and characteristics of the number of chromosomes in AAC, the frequency and spectrum of CA, and the number of MN indicated genotype instability resulting in the abnormalities in hereditary information passing. The localization of chromosomes in the metaphase plate of the lymphocyte culture, which is divided for the first time, corresponds to their state in the interphase nucleus of intact lymphocyte circulating in the body. Therefore, the studies of the frequency of AAC and CA can be extrapolated to the organism level.

The increase in the frequency of AAC, CA in children with iodine deficiency and iron deficiency may serve as a marker of relative immune system deficiency and allows predicting a decrease in its reactivity, which prevents the elimination of cells with an impaired genetic apparatus and requires early administration of appropriate treatment.

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