

Prevalence of Dynamic Mutations Diseases in Bashkortostan Republic (Russia).

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Recently there was described a new group of diseases - dynamic mutations diseases. It is a group of inherited disorders caused by increased number of trinucleotide repeats. The disease develops only when the number of repeats surpasses the definite critical level. They are characterized by various penetrance in combination with incomplete domination; genomic imprinting (difference in phenotypes depending on the sex of the affected parent) and anticipation phenomenon (the earlier onset and more severe manifestation in the subsequent generations). The most interesting examples of dynamic mutation disease are Myotonic Dystrophy (MD) and Huntington's Disease (HD). MD is caused by the expansion of CTG trinucleotide repeats in the long arm of the 19th chromosome [1]. The HD mutation has been identified as an unstable number of CAG repeats located within the coding region of the IT15 gene on the short arm of the 4th chromosome [2, 3]. These trinucleotide repeats are highly polymorphic and do not exceed 30 repeats on chromosomes of unaffected individuals. The range between 30 and 50 repeats is called premutation. Those who have premutation clinically are not affected but they can transfer mutations to the subsequent generations [4, 5].

Mutations could be induced by various mutagens (substances that can cause changes in normal genic structure in human genes). One of the most widespread substances having mutagenic effects which causes problems in many countries is dioxin. "Dioxins" and "furans", frequently named now as a group "dioxins", for the first time have come in the dictionary concerning an environment at the end of 1970 [6]. Nowadays it is clear, that dioxins are not new pollutant, they are formed during burning coal, wood and other substances in household and industrial conditions. The extremely high stability to destruction makes dioxin a universal pollutant, but its highest concentrations are registered in regions with well developed industry. From hygienic and medical positions dioxin problem is explained by great quantity of sources of pollution, stability of dioxins in environment, extremely high toxicity and chronic dioxin intoxication. This causes difficulties in diagnosis and therapy [7]. Dioxin has high lipophilicity, is hardly metabolized, thereof it has strong cumulative effect [8]. Dioxin can realize its biological activity in

decades after direct influence. Even the twenty years' period of time is insufficient for self-restoration of ecotoxic situation in polluted area. Even until the present time it remains dangerous to the population. Dioxin causes remote effects as well. The levels of cytochrome P-450 could be used as a marker in dioxin affected people [7]. Protein complex in a cell and the molecules of working substance influences on nucleic acids and activates synthesis of some proteins. Probably by this way a number of toxic symptoms appears, including infringement of immune reactions of organism [9]. There is no safe dose of dioxin - no freshold below which effects do not occur. Now we know that dioxin acts as a powerful «environmental hormone», disrupting the endocrine system which the body uses to regulate a wide range of physiological functions. Dioxin interferes with the body's natural signaling hormones, resulting as feminization of male offspring, reduces sperm counts, altered sexual behavior, reduced IQ in developing children, weight loss and «wasting» syndrome and suppressed immune system.

Dioxin causes:

- reproductive disorders
- male reproductive disorders: reduces sperm count, testicular atrophy, and abnormal testis structure, reduces size of genital organs, reduces testosterone levels and changes sexual behavior
- female reproductive disorders: decreases fertility, inability to maintain pregnancy, ovarian disfunction, endometriosis and hormonal changes
- birth defects
- increased rates of cancer, including tumors of numerous specific sites and all cancers combined
- impaired neurological development related to cognitive or behavioral deficiencies
- immune suppression
- diabetes
- other effects on liver, thymus, spleen, bone marrow and skin.

Contaminated adult passes dioxin to the fetus while it is still in the womb and to the infant through mother's milk. Both the fetus and the infant are much more sensitive to dioxin than an adult. The complete health impact on the child could not to be expressed until maturity [10]. It is supposed that the developing remote consequences affect all levels, including population [11]. Toxic influence of dioxin on the person is multilateral, it's degree of it is defined by many factors and first of all by the level and duration of contact with toxic agent.

Bashkortostan Republic (BR) is a region in the center of Russia with population more than 4 million people. It's capital is Ufa with more than one million inhabitants. Ufa and Sterlitamak (second big city in BR) are large industrial cities with plenty of the enterprises and factories. Problems with dioxin in BR has appeared because of high development of a petrochemical complex in BR, high density of an arrangement of the chemical enterprises, the localization them in a city boundaries and low level of waste clearing at manufactures. The most environmental aggressive plants such as Factory of synthetic spiritus and "Khimprom" chemical factory are situated in the northern industrial zone of Ufa [12].

The task of our work was to study dynamic mutation diseases in regions with various ecological situations. The prevalence of MD and HD has been studied in the following cities: Ufa, Sterlitamak, Salavat, Belebey, Birsk, Davlekanovo and Oktyabrsky. In this study we used data from our MD register [13] and data obtained from the interregional genetic counselling center (Ufa, BR, Russia). For March 10, 1998 there are 123 alive patients with MD and 105 patients with HD. Thus the prevalences of these diseases in BR are 3.01 for 100 000 citizens and 2.57 for 100 000 accordingly.

In risk group we included Ufa, Sterlitamak and Salavat. In control group we included cities with rather favorable ecological situation: Belebey, Birsk, Davlekanovo, Oktyabrsky. The results of our epidemiological study are presented in tables 1 and 2.

Table 1.

The prevalence of MD in the regions of BR with different environment

City	Population	Patients	Frequency	Prevalence
Ufa	1 079 765	27	1:39 991	$2.5 \cdot 10^{-5}$
Sterlitamak	247 736	7	1:35 391	$2.8 \cdot 10^{-5}$
Salavat	150 760	2	1:75 380	$1.3 \cdot 10^{-5}$
Total (risk group)	1 478 261	36	1:41 063	$2.4 \cdot 10^{-5}$
Belebey	75 573	5	1:15 115	$6.6 \cdot 10^{-5}$
Birsk	34 735	1	1:34 735	$2.9 \cdot 10^{-5}$
Davlekanovo	23 600	2	1:11 800	$8.5 \cdot 10^{-5}$
Oktyabrsky	104 536	0	---	---
Total (control group)	238 444	8	1:29 806	$3.4 \cdot 10^{-5}$

Table 2.

The prevalence of HD in the regions of BR with different environment

City	Population	Patients	Frequency	Prevalence
Ufa	1 079 765	37	1:29 182	$3.4 \cdot 10^{-5}$
Sterlitamak	247 736	5	1:49 547	$2.0 \cdot 10^{-5}$
Salavat	150 760	4	1:30 152	$2.7 \cdot 10^{-5}$
Total (risk group)	1 478 261	46	1:32 136	$3.11 \cdot 10^{-5}$
Belebey	75 573	1	1:75 573	$1.34 \cdot 10^{-5}$
Birsk	34 735	3	1:11 578	$8.6 \cdot 10^{-5}$
Davlekanovo	23 600	1	1:23 600	$4.2 \cdot 10^{-5}$
Oktyabrsky	104 536	4	1:26 134	$3.8 \cdot 10^{-5}$
Total (control group)	238 444	9	1:26 493	$3.4 \cdot 10^{-5}$

So in ecologically polluted cities of BR the prevalence of dynamic mutations diseases is less than in cities with rather favorable ecological situation (1.4 times for MD and 1.2 times for HD) but statistically it is not significant.

Thus it is possible to make a conclusion about absence of reliable relationship between prevalence of MD and HD and ecological situation in regions. The results of our research cannot exclude mutagenous influence of a dioxin on prevalence of MD and HD. The revealed distinctions in prevalence of these two diseases in various cities of BR could be explained by population genetics mechanisms such as gene drift, ancestor's effect, panmixing and gene isolation.

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