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Lanovenko Olena, Fomina Julia

THE FREQUENCY AND STRUCTURE OF CONGENITAL MALFORMATIONS IN RURAL POPULATIONS OF SOUTHERN UKRAINE AND THE ROLE OF GENETIC AND DEMOGRAPHIC FACTORS IN THEIR DISTRIBUTION

Kherson State University, Ukraine

lanovenko2708@gmail.com

In modern conditions of constant population decline and the presence of adverse demographic processes in Ukraine, the urgent task is to identify the most significant genetic and demographic factors affecting the adaptation of the population, as well as monitoring changes in the volume and structure of the genetic load caused by congenital pathology. The frequency of congenital malformations of newborns in the Kherson region increased (from 22.3±5.4 % in 2000-2008 to 40.1 ± 8.2 % in 2009-2017). In recent years, there has been a statistically significant increase in the frequency of hereditary pathology of newborns among the rural population of the region (from 1.09 to 1.95 %).

The total frequency of congenital malformations increased in almost all areas of the Kherson region (from 20.2±1.4, 27 to 27.6±1.3 %) and averaged 30.2±6.4 %. Significant differences in this indicator were found between some nations of the region. Malformations of the circulatory system (28.5 %), musculoskeletal system (26.05 %) and the genitourinary system (15.25 %) occupy a leading place in the structure of congenital pathology. The prevalence of congenital malformations is inversely correlated with the prevalence of spontaneous miscarriages ($r = -0.52 \pm 0.12$; $t_{r=2.4} > t_{05}=2.12$), which indicates the presence of a screening effect that eliminates non-viable genotypes in embryonic period of ontogenesis.

Rural population where the share of interethnic marriages has increased over the years of research, is characterized by a higher prevalence of congenital malformations ($r=0.50 \pm 0.46$; $t=2.3 > t_{05}=2.12$). In population (with an endogamy index of 0.5 and higher), an increase or relative constancy of the proportion of homolocal mono-ethnic Ukrainian marriages and a lower prevalence of congenital malformations among newborns are observed. The level of endogamy does not significantly affect the prevalence of malformations ($r=-0.20 \pm 0.24$; $t_{r=0.8} < t_{05}=2.12$).

A promising area of research is the study of the causes of differences in the prevalence of congenital

malformations among the rural population of the same region with an analysis of the characteristics of the formation of their ethnic structure.

Keywords: congenital malformations, population, ethnic structure.

Research relation to the programs, plans, and department themes. The research is carried out within the framework of the university research work "Directivity of genetic and demographic processes in conditions of depopulation of the south of Ukraine", state registration number 0112U004273.

Introduction. Birth defects represent a diverse group of disorders of prenatal origin that can be caused by defects in a single gene, chromosomal abnormalities, multifactorial inheritance, ecological teratogen, micronutrient deficiency and maternal infections. Congenital anomaly is a defect in morphogenesis in early embryogenesis. Congenital malformations usually prevailed in children born of consanguinity [1].

Although the etiology is unknown in 50% of cases, genetic (30-40%) and environmental (5-10%) components prevail among the majority of known causes [2].

Taking into account the fact that most cases of congenital malformations among all pregnancy outcomes occur in live births, it is the assessment of the prevalence of congenital malformations among living newborns, and not all births that is the most acceptable form of analysis of epidemiological data [3].

The basis of medical and genetic preventive measures aimed at reducing the burden of congenital malformations, chromosomal and genetic diseases is an accurate knowledge of their prevalence in the region, taking into account the population genetic structure of the population, geographical, environmental and hygienic features territories and quality of medical care to the population [4].

The general prevalence of congenital malformations, their structure and the frequency of some specific malformations are different in different maternal

ethnic groups. A study of the prevalence and structure of congenital malformations in different ethnic groups can become the basis for etiological studies and health planning [5].

In modern conditions of constant population decline and the presence of adverse demographic processes in Ukraine, the urgent task is to identify the most significant genetic and demographic factors affecting the adaptation of the population, as well as monitoring changes in the volume and structure of the congenital pathology. The intensity and direction of population transformations should be investigated in the context of the three components of their dynamics: influences on this process of factors of microevolution, genetic-demographic parameters, epidemiology of hereditary and congenital pathology [6].

There are significant differences in the frequency and structure of congenital malformations in newborns in different regions of Ukraine. In the western region and in the northern part of Ukraine in the structure of congenital malformations of newborns the first place is occupied by defects of the musculoskeletal system, in the southern part of Ukraine the main are defects of the cardiovascular system. In the Chernivtsi region the frequency of defects and deformations of the musculoskeletal system exceeds the data both in Ukraine and in other countries approximately by 2.7 times [7].

The presence of differences in the frequency and structure of congenital malformations of newborns in certain regions of Ukraine and in different countries of the world can serve as evidence of the genetic and demographic conditionality of congenital malformations among the causes of their prevalence [4]. However, the question of exactly which factors of the dynamics of the population structure affect the prevalence of congenital pathology and how much this effect is significant remains unresolved.

The purpose of this study was to analyze the dynamics of the prevalence and structure of congenital malformations of newborns in the rural population of the Kherson region based on monitoring studies for an 18-year period (2000-2017) in the region and clarification of the role of genetic and demographic factors in their distribution.

Material and methods. The study was conducted in accordance with the main criteria of the EUROCAT European Register [8]: 1) conducting research in limited populations (accounting for newborns with developmental abnormalities whose parents live in a given locality); 2) accounting for 19 nosological forms.

When calculating the frequency of malformations of the population of Kherson region, we used the materials of the regional medical-statistical register on the total number of newborns born alive and stillborn, as well as on the birth of children with developmental

disabilities, subject to strict registration (medical form 21, 13, 49). The obtained data were processed using standard statistical methods: the calculation of the standard deviation of the error of the mean, the error of the arithmetic average of the characteristic. Statistical calculation of the obtained results (calculation of confidence intervals and the reliability of differences) was carried out using the programs STATISTICA and Microsoft Excel 9-2000.

In order to analyze the influence of certain parameters of the genetic and demographic structure (the level of interethnic marriages, the endogamy index) on the prevalence of congenital malformations and early spontaneous miscarriages among the population of the district populations of Kherson region, the Spearman correlation coefficient between these parameters was calculated. The significance of the differences was evaluated using Student's t-test.

Results and discussion. In Kherson region, isolated single congenital malformations (97.7%) had the largest share and only 2.3% were multiple, including chromosomal abnormalities. In the conditions of reduction of the population of Kherson oblast and reduction of fertility rate, the frequency of congenital developmental defects among newborns has increased (from 22.3± 5.4 % in 2000-2008 to 40.1 ± 8.2% in 2009-2017 (Table 1).

Table 1 – The frequency of congenital malformations among newborns in Kherson region (2000-2017)

District	Years		
	2000-2008	2009-2017	2000-2017
Belozersky	18,9 ± 4,2	53,3 ± 6,3*	36,3 ± 5,3*
Berislavsky	52,5 ± 12,8*	38,4 ± 6,9	45,2 ± 7,0*
V.Aleksandrovsky	27,1 ± 7,4	23,2 ± 6,0	25,2 ± 4,6
V.Lepetichsky	7,3 ± 1,6	21,5 ± 5,2	14,4 ± 3,0*
V.Rogachiksky	13,9 ± 5,3	12,6 ± 3,9	13,3 ± 3,1*
Vysokopolsky	22,0 ± 5,6	36,6 ± 5,7	29,2 ± 4,4
Genichesky	24,0 ± 3,5	11,6 ± 3,3	17,8 ± 2,9*
Golopristsansky	14,1 ± 3,1	45,6 ± 10,0	29,7 ± 6,9
Gornostaevsky	10,8 ± 3,6	16,1 ± 5,2	13,4 ± 3,0*
Ivanovsky	12,2 ± 4,1	29,5 ± 7,3	20,8 ± 4,3
Kalanchaksky	20,0 ± 5,3	22,3 ± 4,3	21,0 ± 3,4
Kakhovsky	23,0 ± 2,8	28,4 ± 2,3	25,7 ± 1,8
N. Serogosy	8,8 ± 1,3	15,2 ± 5,3	12,0 ± 2,9*
Novovorontsovsky	10,7 ± 2,0	15,4 ± 2,2	13,0 ± 1,6*
Novotroitsky	18,2 ± 4,2	22,6 ± 4,1	20,4 ± 2,9
Skadovsky	33,2 ± 5,2*	32,3 ± 6,7	32,8 ± 4,7*
Tsyurupinsky	30,6 ± 3,3*	32,6 ± 2,7	31,2 ± 2,1*
Chaplynsky	17,0 ± 2,2	40,0 ± 27,5	28,6 ± 5,9
Total in the district	20,2 ± 1,4	27,6 ± 1,3	23,8 ± 1,4
Total in the region	22,3 ± 5,4	40,1 ± 8,2	30,2 ± 6,4

Note: * The differences are statistically significant at p <0.05.

The frequency of genetically determined congenital malformations was significantly higher ($1.33 \pm 0.018\%$) than the average in Ukraine ($0.99 \pm 0.014\%$) in Kherson region for the period of 2002-2015. In recent years, there has been a statistically significant increase in the frequency of hereditary pathology of newborns in the rural population of the region (from 1.09 to 1.95%).

The overall frequency of congenital malformations increased in almost all areas of Kherson region (from $20.2 \pm 1.4\%$ to $27.6 \pm 1.3\%$) and averaged $30.2 \pm 6.4\%$. Significant differences in this indicator were found between some populations of the region: the overall incidence of congenital malformations was significantly higher in Belozersky ($36.3 \pm 5.3\%$), Berislavsky ($45.2 \pm 7.0\%$), Skadovsky ($32.8 \pm 4.7\%$), Tsyurupinsky ($31.2 \pm 2.1\%$) districts. On the contrary, the incidence of congenital malformations among newborns was significantly lower in the V.Lepetichsky, V.Rogachiksky, Genichesky, Gornostaevsky, N.Serogosy, Novovorontsovsky districts (12.0-17.8%).

Anomalies of the circulatory system (28.5%), the musculoskeletal system (26.05%) and the genitourinary system (15.25%) occupy a leading place in the structure of congenital pathology in rural population of southern Ukraine. The structure of congenital malformations of newborns contains maxillofacial defects (mainly lip cleft) (4.25%), chromosomal abnormalities (3.35%), digestive system defects (3.75%), malformations nervous system (3.0%) (Figure).

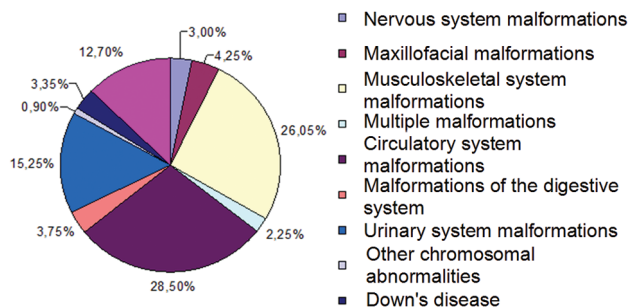


Figure. Structure of congenital malformations of strict accounting (model forms) in the Kherson region (2012-2015)

The proportion of multiple malformations in the overall structure of congenital malformations was 2.27%. In the group of defects with multiple lesions of systems and organs, the proportion of cases with chromosomal pathology and syndromes of other etiology was almost the same – 8.0% and 9.1%, respectively.

In recent years, a statistically significant increase in the frequency of congenital malformations of the circulatory system among all other nosological groups has been observed in Kherson region (from 23.7% for the period of 2000-2006 to 38.3% for the period of 2007-2017). We noted a slight decrease in the fre-

quency of gastrointestinal malformations (from 3.75% to 3.6%), defects of the nervous system (from 3.0% to 2.4%). The frequency of malformations in the development of the urinary organs has remained at the same level (15.5-15.0%). A particular concern is the increase in prevalence in populations of congenital malformations caused by chromosomal aberrations (from 4.2 to 5.3%) and multiple developmental malformations (from 2.1 to 3.4%).

Conclusion and future perspectives. In the context of a decrease in the population of Kherson region and a decrease in the birth rate, the frequency of congenital malformations in newborns increased (from $22.3 \pm 5.4\%$ in 2000-2008 to $40.1 \pm 8.2\%$ in 2009-2017). Significant differences in this indicator were found in the population of the region. The dynamics of the frequency of congenital malformations can be used to assess the adaptive homeostasis of populations under conditions of their genetic and demographic transformation.

The decrease in the frequency of reproductive losses is accompanied by a statistically significant increase in the prevalence of congenital malformations in the population, which can be explained by the selective effect of the "sifting" selection during the period of fetal development ($r = -0.52 \pm 0.12$; $t_r = 2.4 > t_{05} = 2.12$).

The study of dynamics of the structure of congenital malformations showed a statistically significant increase in the prevalence of congenital malformations of the circulatory system among newborns (from 23.7% in the period of 2000-2006 to 35.3% in the period of 2007-2015).

Rural population where the share of interethnic marriages has increased over the years of research is characterized by a higher prevalence of congenital malformations ($r = 0.50 \pm 0.46$; $t = 2.3 > t_{05} = 2.12$), which confirms the validity of the idea of possible negative consequences of outbreeding (violation of adaptive gene complexes, increased recombination rate).

Rural population (endogamy index 0.5 and higher) having an increase or relative constancy of the share of homolocal mono-ethnic Ukrainian marriages is characterized by a lower incidence of congenital malformations among newborns (17.7 ± 3.4 : $19.3 \pm 3.0\%$, respectively) compared with population where the proportion of such marriages has significantly decreased ($28.1 \pm 4.4\%$).

When analyzing the prevalence and structure of congenital and hereditary pathology in population, the influence of population genetic and demographic factors should be taken into account. A promising area of research is the study of the causes of statistically significant differences in the prevalence of congenital and hereditary pathologies among the rural population of one region with an analysis of the characteristics of their ethnic structure and history of formation.

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**ЧАСТОТА І СТРУКТУРА ВРОДЖЕНИХ ВАД РОЗВИТКУ
В СІЛЬСЬКИХ ПОПУЛЯЦІЯХ ПІВДНЯ УКРАЇНИ І РОЛЬ ГЕНЕТИЧНИХ
ТА ДЕМОГРАФІЧНИХ ЧИННИКІВ У ЇХНЬОМУ ПОШИРЕННІ**

Лановенко О. Г., Фоміна Ю.

Резюме. В умовах скорочення населення Херсонської області та зниження народжуваності частота вроджених вад розвитку у новонароджених збільшилася (з 22,3±5,4 в 2000-2008 роках до 40,1±8,2 в 2009-2017 роках). Суттєві відмінності за цим показником виявлені між популяціями регіону. Динаміка частоти вроджених вад розвитку може бути використана для оцінки адаптивного гомеостазу популяцій в умовах їх генетичної та демографічної трансформації.

Зниження частоти репродуктивних втрат супроводжується статистично значущим збільшенням поширеності вроджених вад розвитку в популяціях, що можна пояснити ефектом дії «просюючого» добору в період розвитку плоду ($r=-0,52\pm 0,12$; $t_r=2,4 > t_{05}=2,12$).

Дослідження динаміки структури вроджених вад розвитку показало статистично значуще збільшення поширеності вроджених вад розвитку системи кровообігу серед новонароджених (з 23,7% в період 2000-2006 років до 35,3% в період 2007-2015 років).

Сільські популяції, в яких частка міжетнічних шлюбів за роки досліджень зросла, характеризуються більш високою поширеністю вроджених вад розвитку ($r=0,50\pm 0,46$; $t=2,3 > t_{05}=2,12$), що підтверджує обґрунтованість концепції про можливі негативні наслідки аутбридингу (порушення адаптивних генних комплексів, збільшення швидкості рекомбінації).

Сільські популяції (індекс ендогамії 0,5 і вище), в яких спостерігається збільшення або відносна стабільність частки гомолокальних моноетнічних українських шлюбів, характеризуються більш низькою частотою вроджених вад розвитку серед новонароджених (відповідно 17,7±3,4: 19,3±3,0%) в порівнянні з популяціями, в яких частка таких шлюбів значно знизилася (28,1±4,4) %.

При аналізі поширеності та структури вродженої і спадкової патології в популяціях слід враховувати вплив популяційно-генетичних і демографічних чинників. Перспективним напрямком досліджень є вивчення причин статистично значущих відмінностей в поширеності вроджених і спадкових патологій серед населення сільських популяцій одного регіону з аналізом особливостей їх етнічної структури та історії формування.

Ключові слова: вроджені вади розвитку, популяція, етнічна структура.

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**ЧАСТОТА И СТРУКТУРА ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ
В СЕЛЬСКИХ ПОПУЛЯЦИЯХ ЮГА УКРАИНЫ И РОЛЬ ГЕНЕТИЧЕСКИХ
И ДЕМОГРАФИЧЕСКИХ ФАКТОРОВ В ИХ РАСПРОСТРАНЕННОСТИ**

Лановенко Е. Г., Фомина Ю.

Резюме. В условиях сокращения численности населения Херсонской области и снижения рождаемости частота врожденных пороков развития у новорожденных увеличилась (с 22,3±5,4% в 2000-2008 годах до 40,1±8,2% в 2009-2017 годах). Существенные различия по этому показателю обнаружены между популяциями региона. Динамика частоты врожденных пороков развития может быть использована для оценки адаптивного гомеостаза популяций в условиях их генетической и демографической трансформации.

Снижение частоты репродуктивных потерь сопровождается статистически значимым увеличением распространенности врожденных пороков развития в популяциях, что можно объяснить избирательным действием «просеивающего» отбора в период развития плода ($r=-0,52\pm 0,12$; $t_r=2,4 > t_{05}=2,12$).

Изучение динамики структуры врожденных пороков развития показало статистически значимое увеличение распространенности врожденных пороков системы кровообращения среди новорожденных (с 23,7% в период 2000-2006 гг. до 35,3% в период 2007-2015 гг.).

Сельские популяции, в которых за годы исследований увеличилась доля межэтнических браков, характеризуются более высокой распространенностью врожденных пороков развития ($r=0,50\pm 0,46$; $t = 2,3 > t_{05}=2,12$), что подтверждает справедливость представления о возможных негативных последствиях аутбридинга (нарушение адаптивных генных комплексов, увеличение скорости рекомбинации).

Сельские популяции (индекс эндогамии 0,5 и выше), в которых наблюдается увеличение или относительное постоянство доли гомолокальных моноэтнических украинских браков, характеризуются меньшей частотой врожденных пороков развития среди новорожденных (соответственно 17,7±3,4: 19,3±3,0%) по сравнению с популяциями, в которых доля таких браков значительно снизилась (28,1±4,4) %.

При анализе распространенности и структуры врожденной и наследственной патологии в популяциях следует учитывать влияние популяционно-генетических и демографических факторов. Перспективным направлением исследований является изучение причин статистически достоверных различий в распространенности врожденной и наследственной патологии среди населения сельских популяций одного региона с анализом особенностей их этнической структуры и истории формирования.

Ключевые слова: врожденные пороки развития, популяция, этническая структура.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of coauthors of the article.

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