

УДК 575.17: 599.9

The frequency and structure of congenital malformations in rural populations of southern Ukraine and the role of genetic and demographic factors in their distribution

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Keywords: Congenital malformations, Prevalence, population

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", registered in UkrNTEI (state registration number 0112U004273).

Introduction. The dynamics of the mutational process in populations and deciphering the causes of infertility, spontaneous miscarriages, a heterogeneous group of congenital malformations are the least studied issues of modern human genetics [1].

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 [2].

Although the etiology is unknown in 50% of cases, genetic (30-40%) and environmental (5-10%) components prevail among the majority of known causes [3].

Given 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 [4].

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 [5].

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 [6].

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 [7].

The **aim of this study** - analysis of 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.

Data for study 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 the 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.

Results and their interpretation. In the Kherson region, isolated single congenital malformations (97.7%) have the largest share and only 2.3% are 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 $22.3 \pm 5,4$ ‰ in 2000-2008 to $40,1 \pm 8,2$ ‰ in 2009-2017 (Table 1).

Table 1

The frequency of congenital malformations among newborns in the Kherson region (2000-2017)

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

* The differences are statistically significant at $p < 0,05$

The frequency of genetically determined congenital malformations was significantly higher (1.33 ± 0.018 ‰) than the average in Ukraine (0.99 ± 0.014 ‰) in

the Kherson region for the period 2002-2015 years. 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 increases in almost all areas of the Kherson region (from $20.2 \pm 1.4\text{‰}$ to $27.6 \pm 1.3\text{‰}$) and averaged $30.2 \pm 6.4\text{‰}$. Significant differences in this indicator were found between some populations of the region: the overall incidence of congenital malformations is significantly higher in Belozersky ($36.3 \pm 5.3 \text{‰}$), Berislavsky (45.2 ± 7.0), Skadovsky ($32.8 \pm 4.7 \text{‰}$), Tsyurupinsky ($31.2 \pm 2.1 \text{‰}$) districts. On the contrary, the incidence of congenital malformations among newborns is 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 populations 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%) (**Fig.1**).

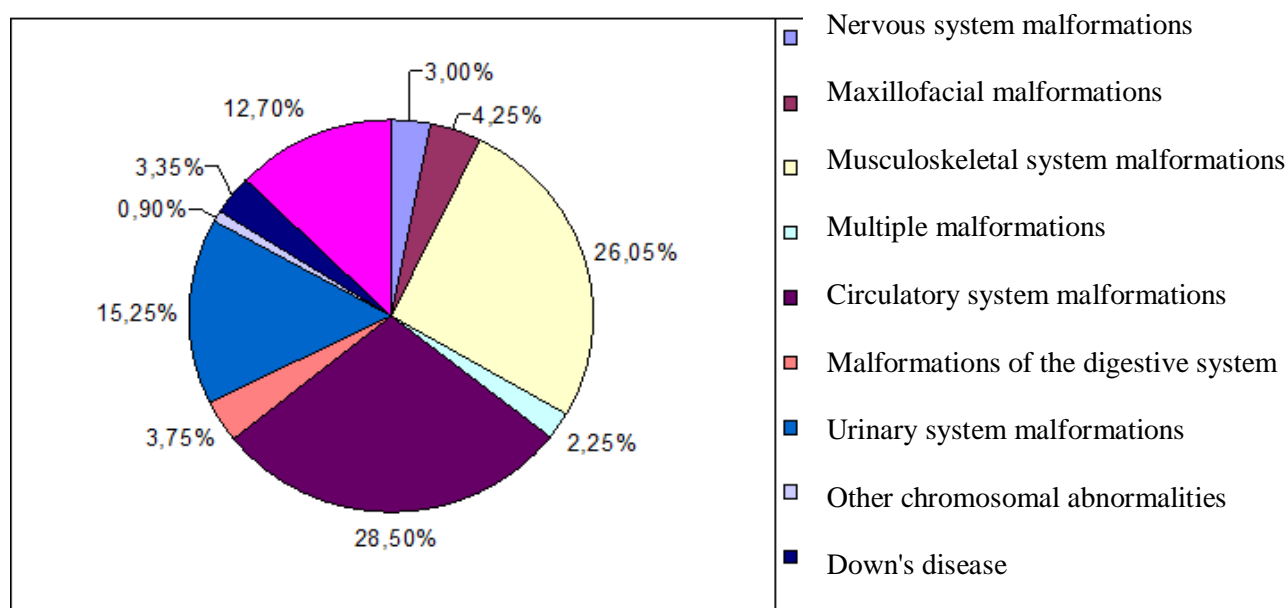


Fig.1. Structure of congenital malformations of strict accounting (model forms) in the Kherson region (2012-2015)

The proportion of multiple malformations in the overall structure of congenital malformations is 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 is almost the same - 8.0% and 9.1%.

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 the Kherson region (from 23.7% for the period 2000-2006 to 38.3% for the period 2007-2017). We noted a slight decrease in the frequency 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 ‰).

Between different regions of Ukraine there are significant differences in the frequency and structure of congenital malformations in newborns. 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 - 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 2.7 times [9].

Conclusions and future perspectives. 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 $22.3 \pm 5,4$ ‰ in 2000-2008 to $40,1 \pm 8,2$ ‰ in 2009-2017). Significant differences in this indicator were found between some populations 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.

A decrease in the population frequency of reproductive losses is accompanied by a statistically significant increased prevalence of congenital malformations in the

population, which can be explained selective action of "sifting" selection during the period of fetal development.

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

The prevalence of congenital malformations in rural populations 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 "sifting" selection effect that eliminates nonviable genotypes in the embryonic period of ontogenesis.

Rural populations, where over the years of research there has been an increase in the share of interethnic marriages, are characterized by a higher average prevalence of congenital malformations ($r = 0.50 \pm 0.46$; $t = 2.3 > t_{05} = 2.12$) and low reproductive losses ($r = -0.27 \pm 0.24$; $t = 1.13 < t_{05} = 2.12$).

Rural populations, which are now elementary populations (endogamy index 0.5 and higher) and in which an increase or relative constancy of the proportion of homolocal mono-ethnic Ukrainian marriages is observed, are characterized by a lower incidence of congenital malformations of newborns (respectively 17.7 ± 3.4 ; $19, 3 \pm 3.0$ ‰) compared with populations in which the proportion of such marriages significantly decreased (28.1 ± 4.4) ‰. The frequency of homolocal Ukrainian marriages is inversely correlated with the prevalence of congenital malformations ($r = -0.37 \pm 0.23$; $t_r = 1.59 < t_{05} = 2.12$), although this relationship is not statistically significant. The level of endogamy does not significantly affect the prevalence of malformations ($r = -0.20 \pm 0.24$; $t_r = 0.8 < t_{05} = 2.12$).

Analyzing the prevalence and structure of congenital and hereditary pathology, it is worth considering the influence of population genetic and demographic factors. A promising area of research is the study of the causes of differences in the prevalence of congenital malformations among rural populations of the same region with an analysis of the characteristics of their ethnic structure.

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Частота і структура вроджених вад розвитку серед сільського населення півдня України і роль генетичних та демографічних чинників у їхньому поширенні

Лановенко О.Г., Фоміна Ю.

У сучасних умовах постійного скорочення чисельності населення і наявності несприятливих демографічних процесів в Україні актуальним завданням є виявлення найбільш значущих генетичних і демографічних чинників, що впливають на адаптацію населення, а також моніторинг зміни обсягу і структури генетичного тягаря, викликаного вродженою патологією. Частота вроджених вад розвитку новонароджених в Херсонській області збільшилася (з $22,3 \pm 5,4$ ‰ в 2000-2008 роках до $40,1 \pm 8,2$ ‰ в 2009 -2017 роках). В останні роки спостерігається статистично значуще збільшення частоти спадкової патології новонароджених серед сільського населення регіону (з 1,09 до 1,95‰). Загальна частота вроджених вад розвитку збільшилася практично в усіх районах Херсонської області (з $20,2 \pm 1,4$ до $27,6 \pm 1,3$ ‰) та в середньому становить $30,2 \pm 6,4$ ‰. Істотні відмінності за цим показником виявлені між деякими популяціями регіону. У структурі вродженої патології провідне місце займають вади розвитку системи кровообігу (28,5%), кістково-м'язової системи (26,05%) і сечостатевої системи (15,25%). Поширеність вроджених вад розвитку зворотно корелює з поширеністю мимовільних викиднів ($r = -0,52 \pm 0,12$; $t_r = 2,4 > t_{05} = 2,12$), що вказує на наявність ефекту відбору «просіювання», який усуває нежиттєздатні генотипи в ембріональний період онтогенезу.

Сільські популяції, в яких за роки досліджень зросла частка міжетнічних шлюбів, характеризуються більш високою поширеністю вроджених вад розвитку ($r = 0,50 \pm 0,46$; $t = 2,3 > t_{05} = 2,12$). В елементарних популяціях (з індексом ендегамії 0,5 і вище) спостерігається збільшення або відносна сталість частки гомолокальних моноетнічних українських шлюбів і більш низька поширеність вроджених вад розвитку серед новонароджених. Рівень ендегамії істотно не впливає на поширеність вад розвитку ($r = -0,20 \pm 0,24$; $t_r = 0,8 < t_{05} = 2,12$).

Перспективним напрямком досліджень є вивчення причин відмінностей у поширеності вроджених вад розвитку серед сільського населення того ж регіону з аналізом особливостей формування їх етнічної структури.

Ключові слова: вроджені вади розвитку, популяція, етнічна структура

Частота и структура врожденных пороков развития среди сельского населения юга Украины и роль генетических и демографических факторов в их распространении

Лановенко Е.Г., Фомина Ю.

В современных условиях постоянного сокращения численности населения и наличия неблагоприятных демографических процессов в Украине актуальной задачей является выявление наиболее значимых генетических и демографических факторов, влияющих на адаптацию населения, а также мониторинг изменения объема и структуры генетического груза, вызванного врожденной патологией. Частота врожденных пороков развития новорожденных в Херсонской области увеличилась (с $22,3 \pm 5,4$ % в 2000-2008 годах до $40,1 \pm 8,2$ % в 2009 -2017 годах). В последние годы наблюдается статистически значимое увеличение частоты наследственной патологии новорожденных среди сельского населения региона (с 1,09 до 1,95%).

Общая частота врожденных пороков развития увеличилась практически во всех районах Херсонской области (с $20,2 \pm 1,4$ до $27,6 \pm 1,3$ %) и в среднем составляет $30,2 \pm 6,4$ %. Существенные различия по этому показателю были обнаружены между некоторыми популяциями региона. В структуре врожденной патологии ведущее место занимают пороки развития системы кровообращения (28,5%), костно-мышечной системы (26,05%) и мочеполовой системы (15,25%). Распространенность врожденных пороков развития обратно коррелирует с распространенностью самопроизвольных выкидышей ($r = -0,52 \pm 0,12$; $t_r = 2,4 > t_{05} = 2,12$), что указывает на наличие эффекта отбора «просеивания», который устраняет нежизнеспособные генотипы в эмбриональный период онтогенеза.

Сельские популяции, в которых за годы исследований возросла доля межэтнических браков, характеризуются более высокой распространенностью врожденных пороков развития ($r = 0,50 \pm 0,46$; $t = 2,3 > t_{05} = 2,12$). В элементарных популяциях (с индексом эндогамии 0,5 и выше) наблюдается увеличение или относительное постоянство доли гомолокальных моноэтнических украинских браков и более низкая распространенность врожденных пороков развития среди новорожденных. Уровень эндогамии не оказывает существенного влияния на распространенность пороков развития ($r = -0,20 \pm 0,24$; $t_r = 0,8 < t_{05} = 2,12$).

Перспективным направлением исследований является изучение причин различий в распространенности врожденных пороков развития среди сельского населения того же региона с анализом особенностей формирования их этнической структуры.

Ключевые слова: врожденные пороки развития, популяция, этническая структура

The frequency and structure of congenital malformations among the rural population of southern Ukraine and the role of genetic and demographic factors in their distribution

Lanovenko E.G., Fomina J.

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 ‰ to 27.6 ± 1.3 ‰) and averaged 30.2 ± 6.4 ‰. Significant differences in this indicator were found between some populations 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 populations, in which the share of interethnic marriages has increased over the years of research, are characterized by a higher prevalence of congenital malformations ($r = 0.50 \pm 0.46$; $t = 2.3 > t_{05} = 2.12$). In elementary populations (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.

Key words: congenital malformations, population, ethnic structure