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RARE DISEASES IN MONITORING OF CONGENITAL ANOMALIES

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REZUMAT

ANOMALIILE RARE ÎN MONITORIZAREA MALFORMAȚIILOR CONGENITALE

Cuvinte cheie: anomalii rare, monitorizare, malformații congenitale, registru internațional "EUROCAT", frecvență, structura malformațiilor congenitale.

Introducere: Malformațiile congenitale (MC) sau anomaliile congenitale (AC) reprezintă tulburări structurale care apar în perioada intrauterină de dezvoltare a fătului. În Republica Moldova (RM), malformațiile congenitale se situează anual pe locul secund în rândul cauzelor mortalității infantile. MC care au o incidență mai mică de 1:2000 sunt considerate malformații rare. Monitorizarea continuă a MC permite determinarea frecvenței tuturor tipurilor de anomalii și aprecierea lor, ca fiind rare sau nu.

Scopul studiului: Compararea frecvenței, structurii și dinamicii MC rare în populația Republicii Moldova cu indicatorii Registrului Internațional European EUROCAT în baza studiilor genetico-epidemiologice (2011-2018).

Materiale și metode: Lucrarea relevă o abordare epidemiologică. Ca instrumente de studiu au fost datele Registrului Național al Republicii Moldova pe perioada anilor 2011-2018 și materialele oficiale ale Biroului Național de Statistică al Republicii Moldova. Pentru compararea datelor statistice, au fost utilizate materiale de pe site-ul oficial al Registrului European EUROCAT. Frecvența malformațiilor congenitale au fost calculate la 1000 de nou-născuți.

Concluzii: În urma analizării structurii MC pe perioada 2011-2018, malformațiile sistemului respirator au fost clasate ca fiind rare cu o frecvență de 0.13:1000 sau 1:7692 de nou-născuți. Conform datelor Registrului EUROCAT malformațiile sistemului respirator se întâlnesc mai des cu 2,6 ori, fiind considerate rare cu o frecvență de 1:2941 de copii. Anencefalie, hidrocefalie, atrezia anusului și esofagului sunt malformațiile congenitale rare care au o incidență mai crescută în RM comparativ cu datele EUROCAT-ului, pe când omfalocele, defecte reducționale, microcefalie și spina bifida au o incidență similară cu indicatorii Registrului European.

РЕЗЮМЕ

РЕДКИЕ БОЛЕЗНИ В МОНИТОРИНГЕ ВРОЖДЕННЫХ АНОМАЛИЙ

Ключевые слова: редкие аномалии, мониторинг, врождённые аномалии развития, Международный регистр EUROCAT, частота, структура ВА.

Введение. Врождённые аномалии (ВА), или пороки развития, представляют собой структурные нарушения, возникающие в период внутриутробного развития плода. В Республике Молдова среди причин младенческой смертности ВА ежегодно занимают второе место. ВА, имеющие распространённость 1:2000 и реже, относятся к редким. Непрерывный мониторинг ВА позволяет определить частоту отдельных аномалий и оценить, относятся ли они к редким болезням.

Цель исследования: На основе генетико-эпидемиологических исследований (2011-2018 гг.) сравнить частоту, структуру и динамику редких ВА в популяции Республики Молдова с показателями Международного Европейского Регистра EUROCAT.

Материалы и методы исследования. В работе использован эпидемиологический подход. Были использованы данные Национального Регистра ВА РМ, осуществляющего мониторинг ВА, за период 2011-2018 гг. Были использованы официальные материалы Национального бюро статистики РМ. Для сравнения и сопоставления статистических данных были использованы материалы с официального сайта Европейского Регистра EUROCAT. Частоты ВА рассчитывались на 1000 новорождённых.

Результаты исследования. На базе данных мониторинга врожденных пороков развития Республики Молдова – Национального регистра Молдовы, сформированного на базе лаборатории профилактики наследственной патологии при Институте Матери и Ребенка, за период с 2011 по 2018 годы установлена средняя частота ВА на 1000 новорождённых – 17,75, по сравнению с EUROCAT – 20,18:1000 новорождённых. В статье представлены результаты сравнительного анализа частоты, структуры и динамики редких ВА в популяции Республики Молдова с показателями Международного Европейского Регистра EUROCAT.

Выводы. Анализ структуры врожденных аномалий за анализируемый период показал, что аномалии дыхательной системы относятся к редким аномалиям, с частотой 0,13:1000 или 1:7692 новорождённых; в Регистре EUROCAT они встречаются в 2,6 раза чаще, но также относятся к редким аномалиям с частотой 1:2941 детей. К редким заболеваниям с частотой, превышающей соответствующие показатели EUROCAT, относятся следующие врождённые аномалии: анэнцефалия, гидроцефалия, атрезия ануса и атрезия пищевода, частоты других редких ВА – омфалоцеле, редукционных пороков, микроцефалии и spina bifida – сопоставимы с аналогичными показателями Европейского Регистра.

Background. Congenital anomalies (CA) or birth defects are structural disorders which arise during fetal development and can be diagnosed before birth or in later stages of a child's' development [1, 2, 3, 4]. Along with perinatal hypoxia, prematurity and infections, CA also contribute significantly to morbidity and mortality in neonatal period [1]. According to the International CA monitoring report, 6% of the annually born children suffers from CA [5]. The share of global neonatal mortality caused by CA increased from 3% in 2008 to 4,4% in 2013 [6, 7]. More than 90% of CA cases have been registered in countries with low or middle income [8]. In the Republic of Moldova (RM) CA is the second leading cause of infant mortality [9].

Although CA are traditionally not considered as rare diseases since, according to current provisions, diseases classified as "rare" if their frequency as low as a 1:2000 and less [10, 11], this frequency is characteristic for the range of CA which, therefore, can be classified as "rare". Continuous and comprehensive CA monitoring can determine the frequency of individual anomalies and appreciate whether they are rare.

CA monitoring in children allow health service workers as on the national as well as on European level to collect and distribute the information which improve knowledge, diagnosis and treatment CA. It is also possible to search for and standardize the collection and exchange of data on CA, which increases the value of each National register and the entire CA registration as a whole [12].

Aim. Based on genetic epidemiological studies carried out in a period from 2011 to 2018 гг.) compare the frequency, structure and changes over time the rare CA in the population of Republic of Moldova with the same variables of International European Register EUROCAT.

Materials and methods. The study uses an epidemiological approach. Were used data of the National CA Registry from Republic of Moldova, which carrying out CA monitoring under the Order issued by Ministry of Health from Republic of Moldova Nr. 1606 dated December 31, 2013: "Concerning Approval the National Program of Prevention and Reducing Mortality and Morbidity in Children Caused by Congenital Anomalies and Hereditary Pathology, 2013 – 2017" [13]. CA have been registered in chidren in the first year of life, as well as using prenatal ultrosonographic diagnosis. Were used official data from the Department of National Bureau of Statistics from Republic of Moldova. To compare and matching statistical data were used materials available online on the Europeam Register EUROCAT official website EUROCAT [12].

The frequencies of congenital anomalies were calculated on 1000 newborns. To make the received data in consistency with variables presented on official EUROCAT website the data grouped for the period from 2011 to 2018.

Results.

Between 2011 and 2018 the mean CA frequency in the population from Republic of Moldova was 17,75 per 1000 newborns, and the same EUROCAT variable was 20,18:1000 newborns, and this variable was subject to fluctuations; so, minimal CA frequency was registered in 2014 (15,38:1000), the maximal value in 2017 (21,84:1000), without the clear trend to increase or decrease (Fig. 1). Thus, during the reviewed period the CA frequencies in the Republic of Moldova and in EUROCAT countries were 1: 56 1:50 newborns, respectively, what suggests high frequency of these anomalies.

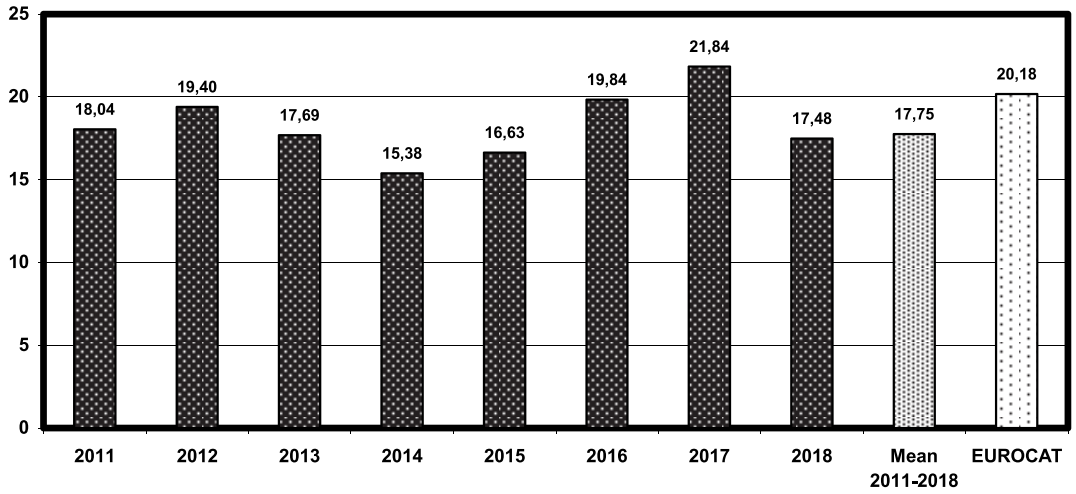

Fig. 1. ***The frequency of congenital anomalies per 1000 newborns, 2011-2018.***

To determine the sharing of CA all registered CA were distributed according to International Classification of Diseases ICD-10 to following groups: CA of nervous system (Q00 – Q07); maxillo facial CA (Q10 – Q18); circulatory CA (Q20 – Q28); respiratory CA (Q30 – Q34); digestive CA (Q35 – Q45); reproductive CA (Q50 – Q64); osteo muscular CA (Q65 – Q79); multiple anomalies et others (Q86 – Q89), as well as chromosomal aberrations (Q90 – Q99).

Table 1.

Структура врождённых аномалий в Республике Молдова и в EUROCAT, 2011 – 2018 гг.

No	Systems of organs:	Republic of Moldova (per 1000 neonates)	Republic of Moldova CA to neonates	EUROCAT (per 1000 neonates)	EUROCAT CA to neonates
1.	Osteo muscular	3,0	1:333	3,79	1:264
2.	Cardio vascular	4,06	1:246	6,78	1:147
3.	Reproductive	0,87	1:1149	2,04	1:490
4.	Multiple CA	3,39	1:295	1,65	1:606
5.	Maxillo facial	1,01	1:1000	1,27	1:787
6.	Digestive	0,69	1:1449	1,45	1:690
7.	Urinary	1,92	1:521	2,91	1:344
8.	Nervous	1,92	1:521	1,17	1:855
9.	Respiratory	0,13	1:7692	0,34	1:2941

The analysis of the CA structure was carried out using the data from the National Register for the period 2011 – 2018 in comparison with the data of the European Register EUROCAT for the respective period. The analysis was shown a high incidence of cardiovascular abnormalities in both registers. In the Republic of Moldova their frequency was 4,06:1000 newborns or 1 to 246 newborns, and in Europe these CA are 1,7 times more often, i. e., 6.78:1000 or 1:147 newborns, so these CA are not rare (Table 1). This discrepancy in the variables analyzed can be explained by the incomplete registration of cardiovascular CA in our country. The second place in the structure was occupied by multiple CA with a frequency of 3,39:1000, i. e., 1:295 newborns, and in the European Register they are twice as often. Third place occupies musculoskeletal CA with a frequency of 3,0:1000, i. e., 1:333 newborns, this variable in EUROCAT is higher, i. e., 3,79:1000 or 1:264 newborns. All three types of CA are not rare in both Republic of Moldova and EUROCAT. The smallest part in the structure of CA in our country is accounted for respiratory CA, i. e., 0,13:1000 or 1:7692 newborns, the same trend was shown in the European Register, i. e., 0,34:1000 or 1:2941 newborns. In EUROCAT the frequency of these anomalies is 2,6 times higher than in Republic of Moldova, the fact what partially can be explained by the incomplete registering as well as by the difficulties of diagnosing such CA in the Republic of Moldova. Thus, respiratory CA systems are rare in both Republic of Moldova and Europe (Table 1, Figure 2).

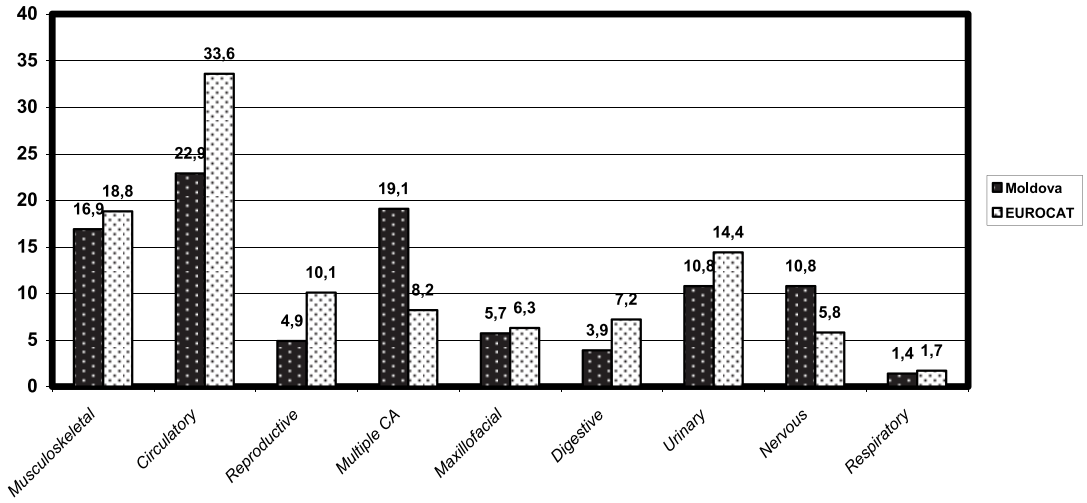

Fig. 2. ***The structure of congenital anomalies in the Republic of Moldova, 2011 – 2018, compared with the data of EUROCAT (%).***

Anomalies of the maxillofacial region were registered in Republic of Moldova and EUROCAT with about the same frequency, i. e., 1,01:1000 and 1.27:1000 newborns, respectively (not rare). Nervous system CA were more frequent in Republic of Moldova than in EUROCAT (1,92:1000 and 1,17:1000, respectively) (not rare). Reproductive CA (0,87:1000 vs. 2,04:1000, respectively), digestive CA (0,69:1000 vs. 1,45:1000, respectively) and urinary CA (1,92:1000 vs. 2,91:1000, respectively) were showed in the structure of CA in EUROCAT almost 2 times more often than in Republic of Moldova. All calculated frequencies of CA were not rare (Table 1).

Among CA special place is occupied by epidemiological indicators of the so-called "sentinel CA" since their importance reflects the state of ecology in the country. Sentinel CA include, among others, spina bifida and anal atresia. The changes of the frequencies of these congenital anomalies were also studied in the presented study.

A study of the frequency of spina bifida per 1000 newborns (Figure 3) showed the frequency of this CA as 0,33:1000 in 2011, 0,30:1000 in 2012, 0,48:1000 in 2013, 0,32:1000 in 2014, 0,16:1000, followed by an increase to 0,45:1000 in 2016 and a maximum of 0,68:1000 in 2017 with subsequent decline in 2018 to 0,28:1000. Thus, the average birth rate of children with spina bifida was 0,38:1000 (1:2632), which is significantly higher than in EUROCAT, i. e., 0,16:1000 (1:6250). Thus, spina bifida is also a rare CA in the Republic of Moldova, but is much more frequent than in Europe. Keeping in mind what this CA refers to folate-dependent, we suppose the ineffective using of folic acid by pregnant women, i. e., flaws in preconceptional prevention and non-compliance to recommendations for folic acid supplementation in the first trimester of pregnancy.

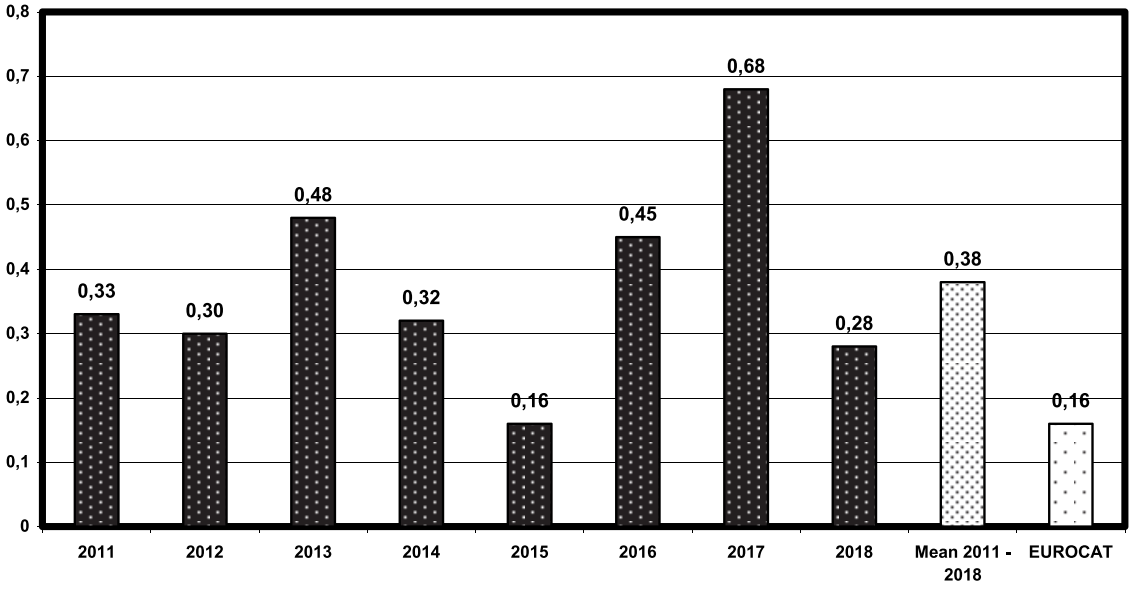

Fig. 3. ***Changes in the frequency of spina bifida for 1000 newborns in Republic of Moldova, 2011 – 2018.***

Taking into account the fact that CA of the central nervous system in live births in the Republic of Moldova are registered almost twice as often as in the EUROCAT (10,8% vs. 6,8%, respectively), the frequency of other nosological forms of CA of nervous system was analyzed, i.e., hydrocephalus, anencephaly and microcephaly (Figure 4).

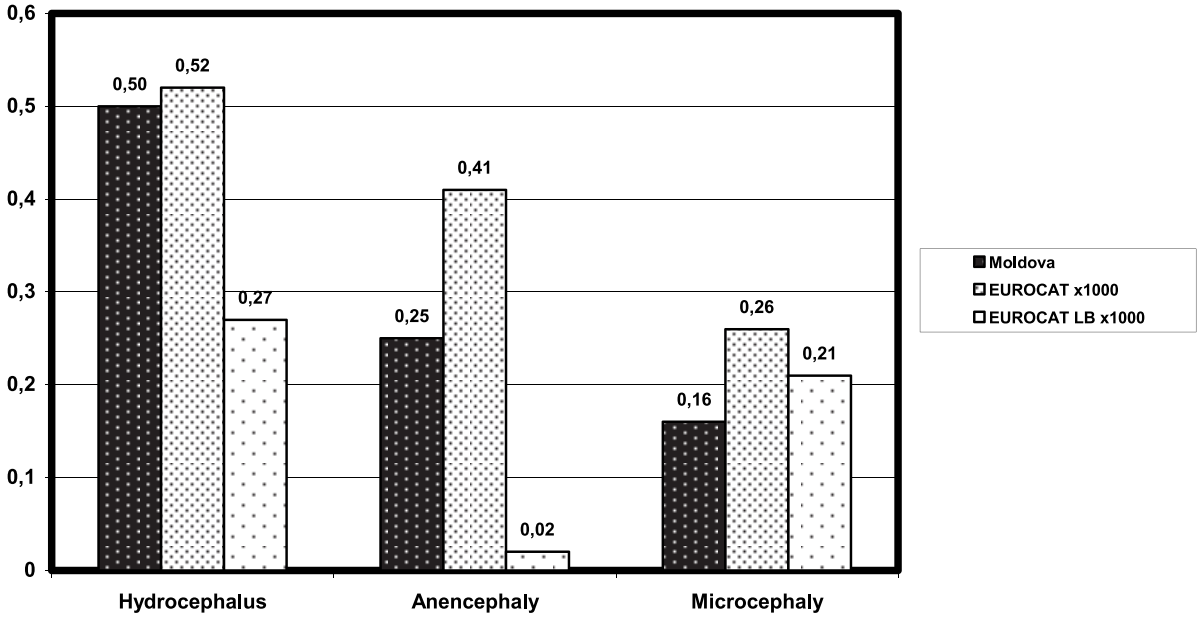

Fig. 4. ***Comparison of frequencies of central nervous system CA in the Republic of Moldova and EUROCAT, years 2016 – 2018, per 1000 children.***

Figure 4 shows the frequency of CA of central nervous system in the Republic of Moldova (column 1), the total frequency of the anomaly in EUROCAT (column 2) and the frequency of this anomaly in live births (column 3). Taking into account the difference between the last two indicators, it is possible to assume the effectiveness of prenatal ultrasound screening, what is especially true in the diagnosis of anencephaly and hydrocephalus. For example, the frequency of anencephaly in Europe is 0,41:1000 fetuses, and the frequency among live births is 0,02:1000 (1:50000). At the same time, in the Republic of Moldova anencephaly is detected at a frequency of 0,25:1000 or 1:4000.

The total frequency of hydrocephalus in Republic of Moldova is very close to the value in EUROCAT, i. e., 0,50:1000 vs. 0,52:1000 fetuses, respectively, but the frequency of this CA per 1000 newborns in EUROCAT is almost twice lower, i. e., 0,27:1000. This indicates effective prenatal diagnosis in Europe. In Republic of Moldova such analysis is complicated by insufficient reliable information about the elimination of fetuses with this pathology. The total incidence of anencephaly is much lower in the Republic of Moldova compared to EUROCAT, i. e., 0,25:1000 vs. 0,41:1000 fetuses respectively, but the frequency of this anomaly in live birth children in EUROCAT is twice lower, i. e., 0,2:1000. The frequency of microcephaly in Moldova (0,16:1000) is slightly lower than the total frequency of this CA in EUROCAT (0,26:1000 fetuses) and the frequency of this anomaly in EUROCAT among live birth children (0,21:1000).

Taking into account the analysis of the CA of central nervous system we can note that all these anomalies are rare in our country – 1:2000 for hydrocephalus, 1:4000 for anencephaly and 1:6250 for microcephaly.

Study of the frequency of anal atresia to 1000 newborns (Figure 5) showed that the frequency of this CA was 0,28:1000 in 2011, increased in 2012 to 0,40:1000, and since 2013 were registered low frequencies of this CA, i. e., 0,10:1000 in 2013, 0,07:1000 in 2014, 0,10:1000 in 2015, 0,05:1000 in 2016, no cases of this CA were reported in 2017, and the lowest frequency of this CA was registered in 2018, i. e., 0,03:1000. The average frequency of anal atresia was 0,13:1000, which was half from the EUROCAT data of 0,26:1000. Thus, anal atresia is rare in the Republic of Moldova with a frequency of 1:7692.

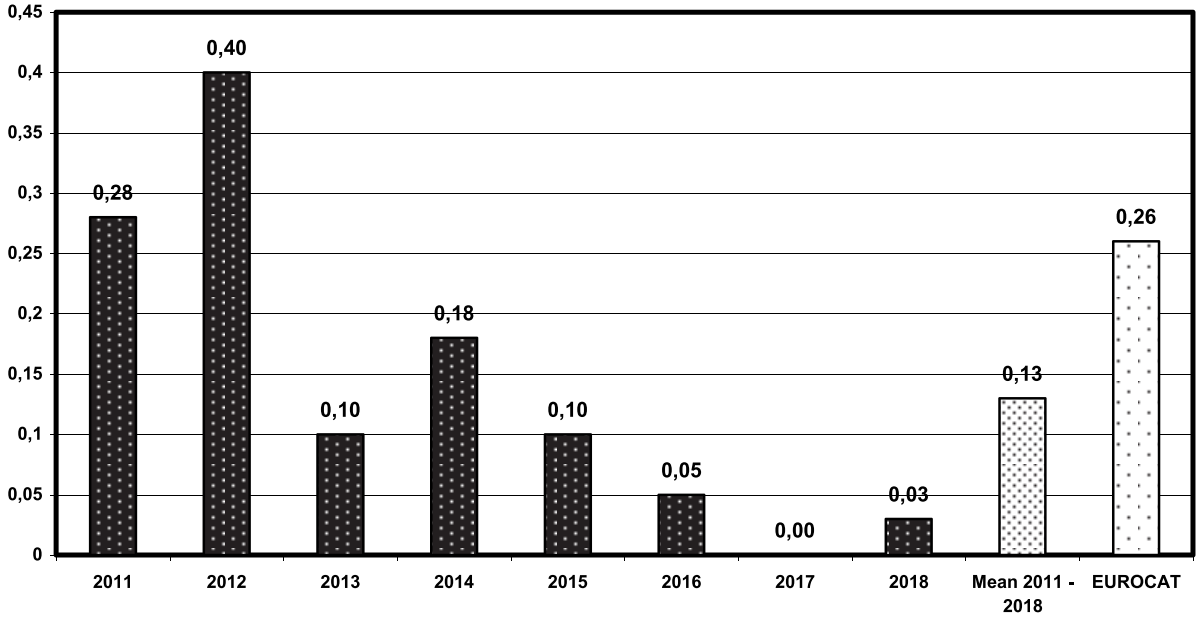

Fig. 5. ***Changes in the frequency of anal atresia, 2011-2018, per 1000 children.***

A comparative analysis of the frequency of sentinel CA in the Republic of Moldova and similar EUROCAT variaqbles from 2011 to 2018 was also carried out for the esophageal atresia, omphalobcele and reduction CA (Table 2).

Table 2.

Frequencies of sentinel congenital anomalies in the Republic of Moldova and EUROCAT, 2011-2018.

	Congenital anomaly type	Data in the Republic of Moldova	Data from the EUROCAT
1.	Anal atresia	1:7692	1:3846
2.	Esophageal atresia	1:8333	1:4167
3.	Omphalocele	1:8333	1:7937
4.	Reduction anomalies	1:2222	1:2994

The data of Table 2 showed that the rare CA in the Republic of Moldova for the studied period are anal atresia with a frequency of 1:7692 newborns, as well as esophageal atresia and omphalogele, which are recorded at the same frequency of 1:8333, and reduction anomalies (1:2222), the fact which coincides with the data of the EUROCAT International Register, in which these congenital anomalies are also rare (Table 2).

Conclusions. Congenital anomalies do not belongs to rare diseases, as between 2011 and 2018 their average frequency in Moldova was 17,75 per 1000 newborns, and the same value was determined in EUROCAT Register, i. e., 20,18:1000.

Analysis of the structure of congenital anomalies during the period analyzed showed that respiratory system anomalies are rare, at a frequency of 0,13:1000 or 1:7692 newborns, bu the data of EUROCAT International European Register, in which these anomalies occurs 2,6 times more often, but also refer to rare abnormalities with a frequency of 1:2941 children.

Rare diseases in our country with a frequency exceeding the corresponding EUROCAT rates include the following birth defects: anencephaly, hydrocephalus, anal atresia and esophageal atresia; the frequencies of other rare CA, i. e., omphalocele, reduction anomalies, microcephaly and spina bifida are comparable to similar variables of the European Register.

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