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SYNTROPY OF UNCLASSIFIED COMPLEXES OF MULTIPLE CONGENITAL MALFORMATIONS

Key words: *multiple congenital malformations, children, syntropy.*

Abstract. *Statistical analysis of unclassified complexes multiple of congenital malformations was performed . Frequency of the most frequent combination of defects consisting of multiple congenital malformations was determined , syntropy index was defined. "Watching congenital malformations" (anus atresia, cleft lip/palate, congenital umbilical hernia, clubfoot) according to the analysis of association and syntropy index can be used as a marker as to congenital heart defects, central nervous system and kidneys.*

Introduction

Unclassified complexes of multiple congenital malformations (MCMF) are treated as a combination of two or more malformations of organs belonging to different systems, but unlike the syndromes of unknown etiology [1]. Hitherto it is possible to make nosological diagnosis of MCMF in about 60% of cases, and other cases are regarded as unclassified systems [2, 5]. It is obvious that some of these complexes are random combination of several defects in one patient. It is believed that the combination of random defects accounts for only a small share in the group of unclassified complexes (approximately 10 %), and most part of the identified MCMF - is new, previously unknown independent nosological form [3]. To clarify the origin of complex MCMF a certain role is played by syntropy phenomenon . The term "syntropy" was first suggested in 1921 by M. Pfaundler and L. von Seht [11], analyzing the problem polipathy (simultaneous occurrence of several diseases in the a patient). According to modern concepts syntropy is a random mix of two pathological conditions (nosology or syndromes) or more, expecting them to be a common pathogenesis [6].

According to the international monitoring programs [9], multiple defects are observed in 13 % of cases, and among children with MCMF different combinations of congenital anomalies are observed in 20-30% of cases. Epidemiological studies of MCMF allow to specify range of phenotypic manifestations of known syndromes and associations [7] or the accidental discovery of new combinations of defects [4]. Thus, according to the results of different Clearinghouse registers a combination of the defects like hypospadia, congenital heart defects and cleft lip occurred significantly more often than theoretically expected value that dictates the need for further research into the causes of identified combinations of congenital malformations [8].

From practice of medical and genetic counsulting it is known that about 50% of the complaints in case of MCMF nosological diagnosis can not be determined and complex defects are regarded as unclassified [2]. As a result complex etiology remains unidentified and the risk of recurrence is estimated empirically (2-4 %), which considerably complicates the choice of adequate reproductive tactics in each case [10].

Objective

To examine the frequency and syntropy of unclassified MCMF complexes.

Material and methods

The material for the study were clinical and genetic data of 403 families who had children with complex of unclassified MCMF registered in the Chernivtsi antenatal center of fetal health and medical genetics. Genetic maps, worke vut for such families during the period 2001-2012 and MCMF register. Were included into analysis. We used clinical and genealogical, cytogenetic, biochemical methods, mathematical modeling. The index was calculated by the syntropy formula Pfaundler M., L. Zeht, 1921: IS = (AxD): (BxC), where IS - syntropy index; A - number of observations from a combination of two types of birth defects; B - population frequency of congenital malformations of the first; C - population frequency of congenital malformations of the second; D - sample size. Evaluation: rate at index greater than 1 - syntropic combination of two defects; when the index is less than 1 - dystropic combination. For a statement as the probability difference generally acceted in biomedical research value of the probability (p) <0,05 was taken into

Table 1

Prevalence of multiple congenital malformations

Congenital malformations	Prevalence (according monitoring data) (‰)												Prevalence (in constituency of unclassified MCMF) (‰)											
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Cleft lip/palate	1,1	1,2	0,8	1,2	0,7	0,3	0,4	1,0	0,7	0,1	0,8	0,5	0,1	0,8	-	0,4	0,2	0,3	0,4	0,9	0,3	0,4	0,1	0,4
Anencephaly	-	0,6	0,2	0,6	0,1	0,2	0,1	0,1	-	-	-	0,1	-	-	-	-	-	-	-	-	-	-	-	-
Spina bifida	0,3	0,2	0,4	0,2	0,2	-	-	0,3	-	0,1	0,2	0,1	-	0,2	-	0,4	-	-	0,2	0,2	0,2	-	0,1	0,2
Hydrocephaly	0,1	0,1	0,5	0,5	0,3	-	0,1	0,1	0,2	0,3	0,2	0,2	0,1	0,4	0,5	0,4	0,4	1,2	0,4	0,8	0,4	0,4	0,3	0,5
Congenital Heart diseases	1,6	2,7	2,3	2,5	3,2	4,1	4,2	7,5	5,9	5,4	5,6	4,5	0,8	3,0	1,9	1,4	1,7	2,1	1,9	3,0	1,7	1,5	1,6	1,9
Esophagus atresia	-	-	-	-	0,2	-	-	0,1	0,1	0,2	0,1	0,1	-	-	-	-	-	0,1	-	-	0,1	0,2	0,1	0,2
Intestinal atresia	0,1	-	0,2	0,1	0,1	0,1	0,1	0,1	0,1	0,1	-	0,1	-	0,4	0,1	0,2	0,1	0,2	0,2	0,1	0,1	0,1	0,1	0,2
Hypospady	0,4	1,5	1,1	1,6	1,4	1,7	2,1	2,3	2,5	2,2	2,3	3,8	0,1	0,1	0,4	0,1	0,3	0,3	0,4	0,2	0,3	0,3	0,3	0,4
Reducing defect	0,2	0,2	0,1	0,2	0,3	0,1	0,1	-	0,1	-	-	0,1	-	0,1	-	-	-	-	-	-	-	-	-	-
Polydactyly	0,6	-	1,2	-	0,3	0,7	0,9	0,3	0,9	1,1	0,4	0,7	0,1	0,3	0,5	0,1	0,1	0,2	0,1	-	0,2	0,2	0,1	0,1
Agenesy and dysgenesy of kindness	0,3	0,1	0,1	-	-	0,1	0,1	-	0,1	0,1	0,9	0,2	0,1	0,1	-	-	-	-	0,1	0,1	0,2	0,1	-	0,5
Umbilical gernia	0,4	-	-	-	0,1	0,1	0,1	-	0,1	-	0,2	0,2	0,2	0,6	-	0,4	0,3	0,2	-	-	0,8	-	0,1	0,1
Gastroshysis	0,1	-	0,1	0,4	0,1	0,2	0,1	0,2	0,1	0,3	-	-	0,1	-	-	-	0,1	0,2	-	0,1	-	0,1	-	-

Table 2

Frequency of combination of different congenital malformations

Congenital malformations	2001– 2006 years									2007 – 2012 years									
	Congenital heart diseases	Cleft lip/palate	Polydactyly	Clubfoot	Gastroshysis	Intestinal atresia	Reducing defect	Congenital defects of kindness	Hydrocephaly	Congenital heart diseases	Cleft lip/palate	Polydactyly	Clubfoot	Gastroshysis	Intestinal atresia	Reducing defect	Congenital defects of kindness	Hydrocephaly
Congenital heart diseases	-	11	4	7	1	3	1	16	11		13	4	9	-	2	-	32	10
Cleft lip/palate	11	-	1	2	-	-	-	1	4	13		-	-	-	-	-	2	4
Polydactyly	4	1	-	-	-	1	-	1	-	4	-	-	-	-	-	-	1	-
Clubfoot	7	2	-	-	-	-	-	3	3	9							3	2
Gastroshysis	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
Intestinal atresia	3	-	1	-	-	-	-	2	-	2	-	-	-	-	-	-	2	-
Reducing defect	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Congenital defects of kindness	16	1	1	3	1	2	-	-	5	32	2	1	3	-	2	-	-	12
Hydrocephaly	11	4	1	3	-	-	-	5	-	10	4	1	2	-	-	-	12	-

account.

Results and discussion

It was determined that the MCMF is a large etiologically heterogeneous group of congenital anomalies, their frequency in the Chernivtsi region for the period of follow-up was 3,8 ± 0,1 % (1:258).

Chromosomal abnormalities (43,1 %) take the first place in structure MCMF , the second one undifferentiated complex of multiple malformations (36,1 %), and then monogenic syndromes (20,8 %), including autosomal-dominant (11,8 %), autosomal-recessive (5,8 %), X-linked (0,7 %) and syndromes with unspecified type of inheritance (2,4 %).

A dominance of hydrocephalia, cleft lip/palate, MCMF, diaphragmatic hernia in boys, anencephaly in girls was determaned.

According to genetic monitoring in Chernivtsi region the first place takes - cleft lip and/or palate, the second - polydactyly, the third - intestinal atresia, the fourth - reducing defects in the structure of unclassified MUVR, while among "strict accounting" defects the first place take cleft lip and/or palate, the second - polydactyly, the third - anencephaly, the fourth - cerebral spinal hernia. This suggests that the cleft lip and/or palate and polydactyly in both groups had the same morphogenetic path formation (Table 1).

When analyzing the association of congenital malformations the combination of heart defects with cleft lip and palate (33 %), with polydactyly (30 %) and hydrocephaly (27 %) had beeb revealed. Defects of the loco-motor system in 46 % of cases indicated to renal agenesia, and in 33 % - congenital heart diseases. The most frequent combination of defects in the structure of unclassified MCMF complexes are presented in the table 2.

Table 3 shows the results of calculation of the syntropy index for the combination of some defects. Nonrandomness of these combinations suggests the possibility of common morphogenetic pathways of these defects.

"Watching congenital malformations" (anus atresia, cleft lip/palate, congenital umbilical hernia, clubfoot) according to the analysis of association and syntropy index can be used as a marker on congenital heart defects, central nervous system and kidneys.

The most common abnormalities of the musculoskeletal system in the structure of MCMF were dysplasia (34,7 %), 30,6 % of which were combined with congenital heart defects and 18,4% - with anomalies of genital organs.

Anomalies of congenital heart defects in the structure of MCMF were in 48,8 % defects - in 51,1 %. Fatal cases of congenital heart disease were characterized by a large number of associated malformations (62,0 %, $p<0,001$), which exceeded the same indicator in greeting MCMF group (51,1 %). The most common birth defects that may determine the prognosis were defects of the digestive system (14,6 % - among lethal MCMF and 0,41 % - among the vital MCMF, $p<0,001$) and musculoskeletal (33,3 % and 12,6 %, respectively, $p<0,001$).

Abnormalities of the central nervous system in the structure of MCMF made 41,1 % and in 58,9 % of cases were characterized by a combination of related defects. In the structure of lethal MCMF their

Table 3

Syntropy index by multiple congenital malformations

Congenital malformations	Index
Polydactyly + cleft lip/palate	0,05
Anus atresia + congenital heart defect	0,07
Anus atresia + defect of kindness	0,09
Congenital heart defect + cleft lip/palate	0,08
Congenital heart defect + defect of kindness	0,08
Congenital heart defect + mickrocephaly	0,05
Syndactyly + cleft lip/palate	0,06
Loco-motor dysplasy + hydronephrosis	0,05
Cleft lip/palate + hydronephrosis	0,07
Umbilical hernia + hydronephrosis	0,07
Clubfoot + hydronephrosis	0,07
Congenital heart defect + loco-motor dysplasy	0,06
Hydrocephaly + defect of kindness	0,48
Congenital heart defect + hypospady	0,33
Congenital heart defect + single kidney	0,05
Congenital heart defect + hydrocephaly	0,05

number was higher - 63,7%.

Conclusions

1. According to genetic monitoring in Chernivtsi region in the structure of unclassified MCMF the first place is occupied by the cleft lip and/or palate, the second - polydactyly, the third - intestinal atresia, the fourth - reducing defects.

2. "Watching congenital malformations" (anus atresia, cleft lip/palate, congenital umbilical hernia, clubfoot) according to the analysis of association and syntropy index can be used as a marker on congenital heart defects, central nervous system and kidneys.

Referenced. 1. Баранов В.С. Цитогенетика эмбрионального развития человека / В.С. Баранов, Т.В. Кузнецова //СПб.: Изд-во Н-Л, 2007. - 640с. 2. Бочков Н.П. Медико-генетическое консультирование по поводу мутагенных и тератогенных воздействий / Н.П. Бочков, Т.А. Рослова, И.И. Якушина // Мед. генетика. 2009. - Т.8, №1 (79). - С.3-8. 3. Гаврилова О.Е. Генетические аспекты нарушений эмбрионального развития у человека / О.Е. Гаврилова, О.Л. Шестовских, Т.А. Казарчук [и др.] // Мед. генетика: материалы V съезда Российского общества медицинских генетиков. 2005. - Т.4, №4. - 170. 4. Зацепин И.О. Распространенность пороков нервной трубки среди новорожденных и плодов в Республике Беларусь. Перспективы профилактики / И.О. Зацепин, И.В: Наумчик, Р.Д. Хмель [и др.] // Мед. генетика. 2009. - №5. - С.351. 5. Плотко И.С. Региональные частоты пороков развития по данным мониторинга новорожденных / И.С. Плотко, Е.Ю. Машнева, В.П. Федотов // Мед. генетика: материалы V съезда Российского общества медицинских генетиков. 2005. - Т.4, №6. - С.252. 6. Пузырев В.П. Генетический взгляд на феномен сочетанной патологии у человека / В.П. Пузырев // Мед. генетика.- 2008.- Т. 7, № 9.- С. 3-9. 7. Родина Н.Е. Хромосомные нарушения у детей с множественными врожденными пороками развития / Н.Е. Родина, В.А. Овсепян // Мед. генетика: материалы V съезда Российского общества медицинских генетиков. 2005. - Т.4, №6. - С.259. 8. Dadvand P. Descriptive epidemiology of congenital heart disease in Northern England / P. Dadvand, J. Rankin, M.D. Shirley [et al.] // Pediatr. Perinat. Epidemiol. 2009. - V.23, №1. -P.58-65. 9. EUROCAT. Central Registry, University of Ulster, 2006. WEB: http: // www.eurocat.ulster.ac.uk/pubdata. 10. Game E. Prenatal diagnosis of severe structural congenital malformations in Europe / E. Game, M. Loane, H. Dolk [et al.] // Ultrasound Obstet. Gynecol. - 2005. V.25, №1. - P.6-11. 11. Pfaundler M. Weiteres uber Syntropie kindlicher Krankheitzustande / M. Pfaundler, L. von Seht // Zeitschr. f. Kinderheilk.- 1921.- Bd. 30.- S. 298-313.

СИНТРОПІЯ НЕКЛАСИФІКОВАНИХ КОМПЛЕКСІВ МНОЖИННИХ УРОДЖЕНИХ ВАД РОЗВИТКУ

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Резюме. Проведений статистичний аналіз некласифікованих комплексів множинних уроджених вад розвитку. Встановлено частоту поєднання найбільш частих вад у складі множинних уроджених вад розвитку, визначено індекс синтропії. "Сторожеві вади" (атрезія анусу, щілина губи/піднебіння, вроджена пупочна грижа, клишоногість) згідно даних аналізу асоціацій та індексу синтропії можна використовувати в якості маркера щодо уроджених вад серця, центральної нервової системи та нирок.

Ключові слова: множинні уроджені вади розвитку, діти, синтропія

СИНТРОПИЯ НЕКЛАССИФИЦИРОВАННЫХ КОМПЛЕКСОВ МНОЖЕСТВЕННЫХ ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ

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Резюме. Проведений статистический анализ неклассифицированных комплексов множественных врожденных пороков развития. Установлено частоту сочетания наиболее частых пороков в составе множественных врожденных пороков развития, определен индекс синтропии. "Сторожевые пороки" (атрезия ануса, расщелина губи/неба, врожденная пупочная грыжа, косолапость) согласно данных анализа ассоциаций и индекса синтропии можно использовать в качестве маркера для врожденных пороков сердца, центральной нервной системы и почек.

Ключевые слова: множественные врожденные пороки развития, дети, синтропия.

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