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CONGENITAL HYDROCEPHALUS IN NORTHERN BUKOVINA: PROBABILITY AND RISK FACTORS

Summary.

Background. Despite the degree of scientific development of the medical science CNS congenital malformations are about 25% of all congenital malformations in children and their proportion in the structure of perinatal and infant mortality to date is about 30%. Therefore, prenatal diagnosis, prevention and prediction of this pathology have a high profile in many countries of the world. Etiologically in addition to genetic disorders the embryogenesis disorders subject to the action of exo- and endotoxins, the infectious factors is a factor of their occurrence. Hydrocephalus is one of the most common congenital malformations of the nervous system in young children. It is diagnosed in 0.1–2.5% of newborns.

Subjects and Methods. The analysis of the congenital hydrocephalus incidence in the Chernivtsi region for 2007–2016 and the comparison of this indicator with some countries according to EUROCAT data were carried out.

Results. According to EUROCAT the population congenital hydrocephalus incidence ranges from 0.11 to 0.57 %. The congenital hydrocephalus incidence in the Chernivtsi region did not exceed the statistics for Ukraine over the studied period, only in 2012 and 2014 this statistics was higher than the national one. Among the analyzed countries the highest overall incidence over the studied period occurred in Ukraine (0.57 ‰) and the lowest – in Portugal (0.11 ‰).

Conclusions. Probable risk factors of the development of congenital hydrocephalus are the presence of TORCH infection in the pregnant woman, spouses living near motorways, unregistered marriage, influence of chemical factors on both male and female, father's rough labour before pregnancy, smoking and serving in the army. Probable factors for preventing congenital hydrocephalus in children are higher education of the parents and folic acid intake in the first trimester of pregnancy. These factors need to be taken into account when planning pregnancy to prevent fetal congenital hydrocephalus.

Key words: congenital hydrocephalus, Chernivtsi region, risk factors, incidence, children.

Abbreviations. CNS – central nervous system, CM – congenital malformations; CT – computer tomography, MRI – Magnetic Resonance Imaging, NSG – neurosonography, OR – Odds Ratio.

Introduction. Since its inception the human society strives for a continuous improvement of the habitat through the introduction of the latest technological processes, operational excellence, transport network and various branches of science and technology development. However, at the same time, annually increasing environmental footprint has a negative impact on the public health – so-called "Ecologically Related diseases" proceed.

Congenital malformations (CM), along with neoplasms, bronchial asthma and some other diseases have been recognized by many scientists as indicators of ecological ill-being of the environment [1; 2].

Dynamics of the change in these indicators progression study in time can be used to conduct a comprehensive assessment of the ecological state of the environment and the quality of life of the population, as well as to assess the efficiency of preventive measures in the region.

The epidemiology and the risk factors for the occurrence of CM referred to the relevance of the study have resulted largely from the growth of this pathology in children, despite the continuous preventive measures. According to the WHO 4–6% of children with CM are born in the world every year, while the mortality rate is 30–40%. Among the newborns the incidence of CM which is occurred immediately after birth ranges from 2.5 to 4.5% and in the light of defects occurred during the first year of life it reaches 5% [3]. According to V.I. Kulakov [4], E.N.Whitby et al. [5], the influence of congenital anomalies on the overall structure of infant mortality is increasing. The studies conducted in different countries have shown that 25–30% of all perinatal losses are associated with anatomical defects in organs. Among the stillborn children CM is diagnosed in 15–20% of cases [1; 3; 6].

Despite the degree of scientific development of the medical science CNS congenital malformations are about 25% of all congenital malformations in children and their proportion in the structure of perinatal and infant mortality to date is about 30% [7;8]. Often associated with the pronounced CNS structural changes the resistant epileptic seizures and crude neurological semiology occur. Therefore, prenatal diagnosis, prevention and prediction of this pathology have a high profile in many countries of the world. Etiologically in addition to genetic disorders the embryogenesis disorders subject to the action of exo- and endotoxins, the infectious factor (herpesvirus, cytomegalovirus, toxoplasma, etc.) is a factor of their occurrence[9;10;11]. This pathology has not only medical, but also state and social significance, which is especially relevant in terms of an unstable demographic situation.

Hydrocephalus is one of the most common CM of the nervous system in infants [1, 4; 12]. It is diagnosed in 0.1–2.5% of newborns [6, 13].

The main etiological factor of progressive hydrocephalus of non-tumor genesis in newborns and infants is congenital hydrocephalus as an isolated defect of the development of the nervous system in combination with other anomalies of the brain and spinal cord [14, 15].

The possibility of early non-invasive diagnosis of progressive hydrocephalus appeared as a result of the active introduction of CT, MRI, ultrasound methods of investigation, in particular, NSG, transcranial dopplerography (TCDG) of the vessels of the brain [16, 17] to the clinical practice.

Thus, according to the literature, NSG is the main method of diagnosis of progressive hydrocephalus in infants, taking into account its advantages, it allows to determine the degree of hydrocephalus, its morphological form, level of occlusion of the liquor pathways, concomitant pathology and also to evaluate the effectiveness of non-surgical treatment, to conduct surgical treatment in a timely manner, to evaluate the effectiveness of liquor scarring surgeries, to identify possible complications [18; 19; 20]. An ultrasound study is extremely important in the antenatal diagnosis of congenital hydrocephalus and associated neural tube defects beginning with the second trimester of pregnancy [7, 21].

The purpose of our work was to study the incidence and the main risk factors for the formation of hydrocephalus in children of Chernivtsi region.

Subjects and Methods.

The research of the frequency of congenital hydrocephalus was conducted in Chernivtsi region at the premises of medical genetic center. The reports of the Chernivtsi Regional Diagnostic Center of the Ministry of Health of Ukraine were used – Form No. 49 (healthy). "Report on the provision of medical and genetic care" No. 141 (2007–2016) approved by the Regulation of the Ministry of Health of Ukraine of 16 June 1993. Also, the data on the number and morbidity of the children population of the region contained in the statistical yearbooks of Chernivtsi region (2007–2016) was analyzed.

For the analysis of the risk factors for the development of the congenital hydrocephalus the retrospective method was used to study the genetic case report forms (f. No. 149/o) approved by the Regulation of the Ministry of Health of Ukraine of 13 December 1999 for 2000–2016. The medical records of 38 children with congenital hydrocephalus (24 boys and 14 girls) aged 0–18

living in the Chernivtsi region were selected. Diagnosis of congenital hydrocephalus for all examined children was made in the neonatal period. The medical records of the 44 children (26 boys and 18 girls) were taken to identify risk factors. The control group was formed on a population basis, since only those children whose parents were permanently residing in the Chernivtsi region were subject to registration. The following data was collected from their parents: their age at the time of pregnancy, social status, pregnancy number, social habits, education, place of residence, place of work, somatic morbidity, presence of FPI, threat of miscarriage, fetal hydrops, hypamnion, loop of cord and gestational age; if the given child was born as a term fetus or as a premature fetus. The gynecological health, abortions and miscarriages in history. Planned or unplanned pregnancy. Folic acid intake in the first trimester of pregnancy and stress. Detection of TORCH infection during pregnancy. The contraceptives and other drugs intake.

The incidence of cases of congenital hydrocephalus was calculated as the ratio of the cases of this pathology registered by the medical genetic service during the given period of time to the number of births and multiplied by 1000:

$$\text{congenital malfunctions frequency} = \frac{\text{congenital malfunction (total)}}{\text{number of newborns}} \bullet 1000$$

The strength of the association of the features under study was determined using the Odds Ratio (OR), which was performed by the formula:

$$OR = \frac{\grave{A}}{\hat{A}} \frac{\tilde{N}}{D}$$

where A is the presence of the congenital hydrocephalus and the feature under the study; B – the presence of a congenital hydrocephalus and the absence of a feature to be studied; C – the absence of a congenital hydrocephalus and the presence of a feature to be studied; D – the absence of a congenital hydrocephalus and the absence of a feature to be studied.

For OR, the confidence interval (CI) was calculated at 95% level of significance. If the odds ratio was less than 1, then the risk was reduced if = 1, then there was no risk, if more than 1, then there was a risk.

For the assertion of the probability of difference, the usual accepted in medical-biological studies value of the probability level (p) <0,05 was taken into account. With such values of "p", the observed changes in the studied attributes are valid for 95 or more cases out of 100.

All data was analyzed by nonparametric methods of variation statistics using the MedCal (2006) computer program [22].

Results.

The analysis of the congenital hydrocephalus incidence in Chernivtsi region for 2007–2016 and the comparison of this indicator with some countries according to EUROCAT data (Table 1) has been carried out.

Table 1

The congenital hydrocephalus incidence among newborns in the Chernivtsi region and according to EUROCAT (per thousand newborns, %)

Region	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Chernivtsi region	0.10	0.10	0.27	0.30	0.27	0.26	0.17	0.60	–	0.29	0.24
Ukraine	0.58	0.68	0.54	0.55	0.41	0.24	0.57	0.45	–	–	0.57
Austria	0.29	0.09	0.29	0.29	0.59	0.00	–	–	–	–	0.26
Croatia	0.82	0.26	–	0.11	–	0.12	0.20	0.21	0.00	–	0.19

Malta	0.26	0.47	0.00	0.00	0.70	0.23	0.72	0.22	–	–	0.33
Norway	0.34	0.18	0.28	0.48	0.26	0.13	–	–	–	–	0.28
Portugal	0.26	0.16	0.00	0.00	0.00	0.00	0.20	0.46	0.00	–	0.11

Discussion.

According to EUROCAT, the population incidence of hydrocephalus in the studied countries varied in the range of 0.11–0.57 ‰.

Table 1 shows that the congenital hydrocephalus incidence in the Chernivtsi region does not exceed the data for Ukraine almost over the studied period, only in 2012 and 2014 it was higher than in the national one. Among the analyzed countries the highest overall incidence rate over the studied period was in Ukraine (0.57 ‰) and the lowest in Portugal (0.11 ‰). In Chernivtsi region (0.24 ‰) congenital hydrocephalus occurred 2.4 times less frequently than in Ukraine (0.57 ‰). According to Table 1, the congenital hydrocephalus incidence was compared with data from Austria (0.26 ‰) and Norway (0.28 ‰). A slightly higher incidence, compared to the Chernivtsi region, occurred in Malta (0.33 ‰). The low congenital hydrocephalus incidence was observed in Portugal (0.11 ‰) and Croatia (0.19 ‰).

During the analysis of risk factors it was found that male sex is a risk factor for the development of congenital hydrocephalus (OR = 1.19). During the analysis of the index number of pregnancy it was found that the third pregnancy is a risk factor for the development of this pathology (OR = 1.69). Unplanned pregnancy and folic acid intake in the first trimester of pregnancy were reliable protection factors of a pregnant woman from birth of a child with congenital hydrocephalus. Prematurity and anemia of pregnancy were risk factors for the development of this pathology (Table 2).

Table 2

The most important risk factors of developing hydrocephalus in children of Chernivtsi region

Risk factor	OR	CI	Difference peobability
Male sex of a child	1.19	0.49–2.90	
Pregnancy:			
I pregnancy	0.59	0.23–1.55	
II pregnancy	0.92	0.33–2.51	
III pregnancy	1.69	0.53–5.40	
Prematurity	3.57	1.02–12.54	
Unplanned pregnancy	0.22	0.08–0.56	p<0.05
Folic acid intake in the first trimester of pregnancy	0.37	0.15–0.90	p<0.05
Anemia of pregnancy	1.59	0.66–3.83	
Threatened miscarriage	0.48	0.18–1.25	
Recent pregnancy gestosis	1.40	0.48–4.07	
TORCH infection in pregnant	3.60	1.13–11.43	p<0.05
Drug intake during pregnancy	0.96	0.27–3.44	
Fetal hydrops	4.74	0.92–24.41	
Hypamnion	0.57	0.05–6.52	
Social factors:			
The spouses live with parents	1.30	0.54–3.12	
Insufficient family income	1.41	0.57–3.45	
The family lives near motorways	7.02	2.27–21.69	p<0.05
Multi-national marriage	2.08	0.62–7.01	
Mother's age at the time of pregnancy:			
Less than 18 years	3.69	0.37–37.01	
26–35 years	0.40	0.14–1.18	

More than 35 years	3.09	0.74–12.91	
Father's age at the time of impregnation:			
Less than 18 years	0.57	0.05–6.52	
26–35 years	0.80	0.28–2.26	
More than 35 years	1.17	0.22–6.18	
Mother's education			
Secondary	2.43	0.95–6.19	
Incomplete secondary	8.06	0.92–70.32	
Secondary special	0.06	0.01–0.47	
Higher	0.17	0.05–0.56	
Influence of physical factors during pregnancy	0.97	0.38–2.41	
Living in the city	0.97	0.38–2.41	
Living in the country	0.99	0.40–2.48	
Unregistered marriage	9.95	1.96–50.53	p<0.05
Mother's social status – a worker	1.96	0.76–5.02	
Mother's rough labour during pregnancy	6.52	1.31–32.40	
Mother's psychoemotional stress	1.06	0.38–2.95	
Influence of chemical factors during pregnancy	17.14	5.06–58.13	p<0.05
Female smoking	1.46	0.41–5.24	
Coffee overuse during pregnancy	0.64	0.21–0.96	
Alcohol overuse during pregnancy	1.03	0.43–2.46	
Father's education			
Secondary	0.97	0.41–2.32	
Incomplete secondary	8.06	0.92–70.33	
Secondary special	2.08	0.62–7.01	
Higher	0.22	0.07–0.67	p<0.05
Father's social status – a worker	4.50	1.69–11.99	p<0.05
Influence of physical factors on father before pregnancy	2.27	0.85–6.08	
Father served in the army before conception	8.67	2.81–26.78	p<0.05
Father's rough labour before conception	3.64	1.34–9.88	p<0.05
Father's psychoemotional stress	0.99	0.30–3.25	
Influence of chemical factors on the father before pregnancy	37.50	10.32–136.3	p<0.05
Male smoking	3.00	1.22–7.39	p<0.05
Coffee overuse during pregnancy	0.73	0.23–2.28	
Alcohol overuse during pregnancy	0.91	0.32–2.33	

As clinical work has shown the formation of CNS defects in a child is most often associated with intrauterine infection with herpesviruses, cytomegalovirus and also respiratory viruses, whereas the connection of toxoplasmic and mycoplasma infections with central nervous system disorders in a child is discussed [1; 23; 24]. The viral infections of herpes and CMV are a trigger for the development of hypoxic-ischemic lesions of placenta, which makes it possible to transmit the virus from mother to fetus. In our study, the presence of TORCH infection in pregnant women is a reliable risk factor for the development of congenital hydrocephalus (OR = 3.60).

When analyzing the amount of amniotic fluid it was found that in the presence of fetal hydrops there is a high risk of developing this CNS pathology in a child (OR = 4.74). Also, this factor may indicate that a woman has an infection.

The social factors may also be a risk factor for the development of this pathology. So, in our study, it was found that when a family lives close to the motorway, there is a significant risk

of developing a congenital hydrocephalus (OR = 7.02). Other social factors, such as: future parents are living together with their parents, insufficient family income and multi-national marriage are also risk factors of this pathology. It should be noted that according to other authors inter-ethnic marriages, including as a result of migration, are widespread in Ukraine and in their various populations can account for about the half of all marriages [25, 26, 27, 28] and in general are inherent in the Slavic population [29].

The age of mother and father at the time of conception of a child plays an important role in the development of CM, namely, congenital hydrocephalus. Thus, we have shown that the young age of a mother (under 18 years of age) and an elderly mother and father (over 35 years) represent a risk factor for the CNS pathology. In different regions of Ukraine there is a tendency to increase the variance of the age of getting married and this indicator depends on the degree of urbanization of a particular population [30, 31, 32, 33].

The education of parents also plays a role in the development of this pathology. This can be explained by the attitude of spouses to pregnancy, planning of the future child, prevention of the impact of various physical and chemical factors, as well as critical view of bad habits. Thus, it has been shown that higher education of parents is a protection factor against the development of this pathology and mother's secondary and incomplete secondary education and father's incomplete secondary and special secondary education are risk factors of congenital hydrocephalus. Marriage assortativity can play a potential influence on the health of descendants and this phenomenon has also been studied in the Ukrainian and Slavic populations [34].

Also the registration of marriage plays an important role for women. When pregnant in an unregistered marriage a woman experiences constant stress, which is one of the reliable risk factors for the development of this central nervous system malfunction (OR = 9.95). The social status of the spouses plays an important role in the development of this pathology. Thus, with the social status of the "worker" of mother and father, as well as in the rough labour, there is a significant risk factor for the development of congenital hydrocephalus. The risk factor is the fact that father was in the army before pregnancy. Perhaps this is associated with chronic stress and rough labour in the conditions of this service.

The effect of chemical factors on mother and father before and during pregnancy is a reliable risk factor for this CNS pathology. We analyzed the influence of harmful habits on the development of this pathology. So, mother's risk factors include smoking and alcohol abuse before and during pregnancy. In father, the risk factor is only tobacco smoking.

Consequently, the congenital hydrocephalus incidence in children of Chernivtsi region is low, compared to Ukraine and is on average 0.24 ‰ per study period. Probable risk factors of the development of congenital hydrocephalus are the presence of TORCH infection in the pregnant woman, spouses living near motorways, unregistered marriage, chemical factors exposure on both male and female, father's rough labour before pregnancy, smoking and serving in the army. Probable factors for preventing congenital hydrocephalus in children are higher education of the parents and folic acid intake in the first trimester of pregnancy. These factors need to be taken into account when planning pregnancy to prevent fetal congenital hydrocephalus.

It should be noted that the research we have undertaken is harmoniously associated with a number of recent studies generally aimed at increasing the genetic culture of Ukrainian population [35, 36].

Conflict of interest statement.

The authors state that there is no conflict of interest statement in research, authorship and publication of this article.

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