MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE SUMY STATE UNIVERSITY MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

Rymskogo-Korsakova st., Sumy 40007, Ukraine e-mail: EUMJ@med.sumdu.edu.ua eumj.med.sumdu.edu.ua ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2021;9(4):352-361

Abstract

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PERINATAL AND HEREDITARY RISK FACTORS OF HEART RATE AND CONDUCTION DISORDERS IN CHILDREN WITH GASTROESOPHAGEAL REFLUX

Objective: to improve the early diagnosis of cardiac arrhythmias and conduction disorders in children with gastroesophageal reflux by evaluating hereditary and perinatal risk factors for this pathology.

Materials and Methods. The study involved 56 children aged 8 to 18 years, with an average age of 13.67 ± 2.67 years; 28 children with gastroesophageal reflux in combination with arrhythmias and cardiac conduction disorder comprised Group I (the main group), and 28 children with only gastroesophageal reflux without disorders of heart rhythm and conduction comprised Group II (the control group). Patients underwent clinical, anamnestic (with special attention paid to hereditary and perinatal history) and instrumental studies (electrocardiography, 24-hour Holter ECG monitoring, esophagogastroduodenoscopy).

Results. Genetic burden of cardiovascular disease was found in 57.1% of mothers and 42.9% of fathers of patients in the main group, which was significantly higher than that in the control group: by 3.2 times (17.9%; $p \le 0.001$) and 2 times (in 21.4%; $p \le 0.05$), respectively.

Apart from that, stratification of the parameter by the number of chronic diseases, namely ≤ 1 and ≥ 2 , in both parents, showed that fewer (≤ 1) chronic diseases were characteristic of mothers and fathers of the control group children and were registered in 53.5% and 58,9% of them, respectively, while in the main group, the proportion of such parents was lower: by 5 times (10.7%; p \leq 0.001) and 1.8 times (32.1%; p \leq 0.05), respectively.

It was found that gravida 1 para 1 and gravida 2 para 2 mothers were significantly more common among those of patients in the control group (85.8% and 62.5%, respectively; $p \le 0.05$), while gravida 3 para 3 and more was typical for mothers of patients in the main group and were observed in 37.5% of them, while in the control group, this value was 2.6 times lower (14.2%; $p \le 0.05$).

As for the parity, the first childbirth was reported in 64.3% of mothers in the main group and in 28.6% of mothers (2.2 times less often) in the control group (p \leq 0.05); while multipara mothers were characteristic of the control group children (71.4%), which was 2 times more often than in the main group (35.7%; p \leq 0.05).

The risk factors of arrhythmias and cardiac conduction disorder were threatened miscarriage and toxemia in the first half of pregnancy. Thus, threatened miscarriage was reported in 46.4% of mothers of the main



group children and was observed 2.2 times less often (21.4%; $p \le 0.05$) in the control group; toxemia in the first half of pregnancy was diagnosed in 50% of mothers of children in the main group and 2 times less often (in 25%; $p \le 0.05$) – in the control group.

Another predictor of the studied pathology was the physiological course of childbirth. Complicated childbirth was observed in 60.7% of mothers in the main group and 1.9 times less often (32.9%; $p \le 0.05$) – in the control group.

Relatively low (up to 3000 g) birthweight and fetal macrosomia (\geq 4000 g) also acted as risk factors. The proportion of patients with a bodyweight of up to 3000 g was 32.1% in the main group, and 3 times less (10.7%; p \leq 0.05) – in the control group. The bodyweight of \geq 4000 g (large fetus) was a specific feature of patients in the main group, as it was reported exclusively among them (17.9%) and was not observed in the control group (0%, p \leq 0.001).

Conclusions. It was revealed that the maternal and paternal genetic burden of cardiovascular diseases and the number of chronic diseases in parents were statistically significant hereditary risk factors for the development of arrhythmias and conduction disorders in children.

It was found that statistically significant perinatal predictors of arrhythmias and conduction disorders in children with GER included threatened miscarriage; toxemia; multigravida and multipara status; complicated delivery; relatively low (up to 3000 g) birthweight and fetal macrosomia (≥ 4000 g).

Keywords: perinatal and hereditary risk factors, gastroesophageal reflux, arrhythmias, children.

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Резюме

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ПЕРИНАТАЛЬНІ І СПАДКОВІ ФАКТОРИ РИЗИКУ ВИНИКНЕННЯ ПОРУШЕНЬ СЕРЦЕВОГО РИТМУ ТА ПРОВІДНОСТІ У ДІТЕЙ З ГАСТРОЕЗОФАГЕАЛЬНИМ РЕФЛЮКСОМ

Мета: удосконалити раню діагностику порушень серцевого ритму та провідності у дітей з ГЕР, шляхом вивчення спадкових і перинатальних факторів ризику виникнення даної патології.

Матеріали та методи. В дослідженні приймали участь 56 дітей віком від 8 до 18 років, середнім віком $13,67 \pm 2,67$ років, з них 28 дітей з наявністю ГЕР в комбінації з порушеннями серцевого ритму та провідності представляли собою І групу (основну), а 28 дітей з наявністю лише ГЕР без порушень серцевого ритму та провідності — ІІ групу (контрольну). Пацієнтам були проведені клінічні, анамнестичні (особливу увагу приділено спадковому і перинатальному анамнезу) й інструментальні дослідження (електрокардіографія, холтерівське добове моніторування ЕКГ, езофагогастродуоденоскопія).

Результати. Генетичне обтяження з боку серцево-судинних захворювань виявлялось у 57,1 % матерів і у 42,9 % татусів хворих основної групи, що достовірно вище групи контролю (відповідно в 3,2 рази (у 17,9 %; $p \le 0,001$) і в 2 рази (у 21,4 %; $p \le 0,05$).

Крім того, у обох батьків, при укрупненні градації показника кі-



лькості хронічних захворювань до ≤ 1 і ≥ 2 було визначено, що маленька кількість (≤ 1) хронічних захворювань була характерна для матерів і татусів дітей контрольної групи і зареєстрована відповідно у 53,5 % і 58,9 % з них, а в основній групі частка таких матерів і татусів була нижче відповідно в 5 разів (10,7 %; $p \leq 0,001$) і в 1,8 разів (у 32,1 %; $p \leq 0,05$).

Визначено, що перша або друга черговість вагітності, від котрої народилась дитина, достовірно частіше виявлялися серед матерів у хворих групи контролю (відповідно у 85,8 % та 62,5 %; $p \le 0,05$), а третя та більше вагітності були характерні для матерів хворих основної групи і відмічалися у 37,5 % з них та в 2,6 разів рідше (у 14,2 %; $p \le 0,05$) — в групі контролю.

Що стосується черговості пологів, то перші пологи виявлені у 64,3 % матерів дітей основної групи та у 2,2 разів рідше (у 28,6%; р \leq 0,05), в групі контролю, а повторнородящі були характерні для групи контролю та виявлялись у 71,4 % з них і у 2 рази рідше (у 35,7 %; р \leq 0,05) — в основній групі.

Факторами ризику розвитку порушень серцевого ритму та провідності також є загроза переривання вагітності та явища гестозу першої половини вагітності. Так, загроза переривання вагітності діагностована у 46,4 % матерів пацієнтів основної групи та у 2,2 рази рідше (у 21,4 %; р \leq 0,05) — в групі контролю, а гестоз першої половини вагітності відмічався у половини (50 %) матерів хворих основної групи та в 2 рази рідше (у 25 %; р \leq 0,05) — серед матерів дітей групи контролю.

Ще одним предиктором досліджуваної патології ε фізіологічність пологів. При цьому ускладнені пологи були характерні для хворих основної групи, так як виявлялись у 60,7 % з них, і в 1,9 рази рідше (у 32,9; р \leq 0,05) — в групі контролю.

Відносно низька (до 3000 г) вага тіла і великий плід (\geq 4000 г) також є факторами ризику. Доля хворих основної групи з вагою тіла до 3000 г склала 32,1%, а групи контролю – в 3 рази менше (10,7 %; р \leq 0,05). Значення ваги тіла \geq 4000 г (великий плід) виявилось специфічною ознакою для пацієнтів основної групи, так як визначалось лише серед них (у 17,9 %) та не відмічалось в групі контролю (0 %, р \leq 0,001).

Висновки. Виявлено, що достовірними спадковими факторами ризику виникнення досліджуваної патології по лінії обох батьків ϵ генетичне обтяження з боку серцево-судинних захворювань і кількість хронічних захворювань.

Визначено, що достовірними перинатальними предикторами порушень серцевого ритму та провідності в комбінації з ГЕР ϵ черговість вагітності і пологів, від якої народилась дитина; фізіологічність останніх; загроза переривання вагітності; явища гестозу першої половини вагітності; відносно низька (до 3000 г) вага тіла новонародженої дитини і великий плід (\geq 4000 г).

Ключові слова: спадкові і перинатальні фактори ризику, гастроезофагеальний рефлюкс, аритмії, діти.

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How to cite/ Як цитувати статтю: Herasymova OM, Savvo VM. Perinatal and hereditary risk factors of heart rate and conduction disorders in children with gastroesophageal reflux. *EUMJ*. 2021;9(4):352-361 DOI: https://doi.org/10.21272/eumj. 2021;9(4):352-361

Introduction/BCTYII

In recent decades, the proportion of arrhythmias and cardiac conduction disorders has increased significantly in the structure of cardiovascular diseases in children around the world. Various scientists reported that it accounted for up to 30% of all cardiovascular diseases [1, 2].

In childhood, the diagnosis of arrhythmias and conduction disorders is often complicated by asymptomatic course, which is a serious problem because late diagnosis leads to more severe complications and worse pathological process with frequent chronicity and increased risk of sudden death [3, 4].

Differential diagnosis of arrhythmias and conduction disorders in combination gastroesophageal reflux in children is even more challenging, because some pathologies (e.g. chronic gastroduodenitis) accompanied by GER often have asymptomatic course as well, while clinical atypical cardiac manifestations of other diseases (e.g. gastroesophageal reflux disease) are often similar to clinical manifestations of arrhythmias conduction disorders. It is also difficult differentiate between the isolated course of arrhythmias and heart disorders in children in combination with gastroesophageal reflux [5, 6].

An analysis of the scientific data revealed that regardless of the course of pregnancy, the risk of arrhythmias and conduction disorders in children was closely related to their hereditary and perinatal history [7, 8].

However, the role of hereditary and perinatal factors in the development of arrhythmia and conduction disorder combination in children with concomitant gastroesophageal reflux has been insufficiently studied. Therefore, determination of the risk of this pathology in children depending on genetic burden will contribute to early diagnosis and differential diagnosis with isolated variants of arrhythmias and cardiac conduction disorders and digestive diseases accompanied by GER (i.e. gastroesophageal reflux disease and chronic gastroduodenitis). This paper is focused on these issues.

The objective of the paper is to improve the early diagnosis of cardiac arrhythmias and conduction disorders in children with gastroesophageal reflux by evaluating hereditary and perinatal risk factors for this pathology.

Materials and Methods

The study involved 56 children aged 8 to 18 years, with an average age of 13.67 ± 2.67 years, who were inpatients at the City Cardiorheumatology Department of Municipal Non-Profit Enterprise "Children's Clinical Hospital No. 24" of Kharkiv City Council and outpatients at Municipal Non-Profit Enterprise "City Children's Polyclinic No. 23" of Kharkiv City Council in the period from September 2018 to July 2021. Of these, 28 children with gastroesophageal reflux in combination with cardiac arrhythmias and conduction disorder comprised Group I (the main group), and 28 children with only gastroesophageal reflux without disorders of heart rhythm and conduction comprised Group II (the control group).

The patients in the groups were matched by sex: Group I involved $(64.3 \pm 9.1)\%$ of boys, and $(35.7 \pm 9.1)\%$ of girls ($\chi 2 = 0.571$; p = 0.4497 > 0.05); Group II included $(42.9 \pm 9.4)\%$ of boys and $(57.1 \pm 9.4)\%$ of girls ($\chi 2 = 2.286$; p = 0.1306 > 0.05).

During the study, we adhered to the principles of the Declaration of Helsinki of the General Assembly of the World Medical Association (1964–2000) and the protocol of the Bioethics Commission of the Kharkiv Medical Academy of Postgraduate Education No. 2 dated 14 Sep 2021. Informed consent was obtained from all parents or guardians of children who participated in the study.

The inclusion criteria were: 1) gastroesophageal reflux in combination with or without cardiac arrhythmias and conduction disorders, 2) 8 to 18 years of age, 3) signed parent/guardian informed consent form.

Clinical trials were a survey of patients for the presence or absence of relevant complaints that were characteristic of the studied pathology and their further detail: nature, frequency, severity, duration, and the number of identified complaints.

Anamnestic studies included a thorough study of perinatal, hereditary, and life history. Gastroesophageal reflux was confirmed using esophagogastroduodenoscopy. Verification of arrhythmias in children was performed on the basis of electrocardiographic data and 24-hour Holter ECG monitoring with "Poli-Spectr + DM" device.



Exclusion criteria were: congenital heart diseases; acute inflammatory processes during the study; condition after correction of congenital heart disease or radiofrequency catheter ablation; decompensation stage of severe somatic pathology; the refusal of parents or guardians for the children to participate in the study.

Statistical processing of the results was performed using MS Office Excel software (Microsoft Corporation, USA) and Epitools online statistical calculator (epitools.ausvet.com.au, Austria). The age of patients was estimated by determining the sample mean value and the standard error. The frequency of occurrence of the trait (p) was used to describe qualitative variables. Differences in the compared groups were determined using the angular Fisher φ-transformation.

Table 1 – Maternally inherited genetic burden

Homogeneity of gender distribution in groups was tested by means of Pearson's chi-squared test for one-way frequency tables. All calculations were performed with a 95% confidence interval.

Results

The study of the influence of hereditary factors on this pathology showed a significant difference for several maternally inherited parameters (Table 1). Such parameters, first of all, included the genetic burden for cardiovascular diseases. This burden was found in 57.1% of mothers in the main group and in 17.9% of mothers (2.3 times less often) in the control group (p \leq 0.001); while no such burden, on the contrary, was characteristic of the mothers of the control group children (87.1%), which was 1.9 times more often than in the main group (42.9%; p \leq 0.001).

Parameter	Parameter	Group I		Group II		p
	option	n	%	n	%	Р
Cardiovascular diseases	present	16	57.1	5	17.9	≤ 0.001
	absent	12	42.9	23	82.0	≤ 0.001
Gastrointestinal diseases	present	9	32.1	10	35.7	≥ 0.05
	absent	19	67.9	18	64.3	≥ 0.05
Endocrine diseases	present	5	17.9	4	14.3	≥ 0.05
	absent	23	82.1	24	85.7	≥ 0.05
Allergic manifestations	present	7	25.0	3	10.7	≥ 0.05
	absent	21	75.0	25	89.3	≥ 0.05
Vegetovascular disorder	present	5	17.9	3	10.7	≥ 0.05
	absent	23	82.1	25	89.3	≥ 0.05
Obesity	present	11	39.3	8	27.1	≥ 0.05
	absent	17	60.7	20	72.9	≥ 0.05
Urinary system diseases	present	7	25	3	10.7	≥ 0.05
	absent	22	78.6	23	82.1	≥ 0.05
Number of chronic diseases	0	0	0	2	7.1	≥ 0.05
	1	3	10.7	13	46.4	≤ 0.001
	2	13	46.4	7	25.0	≥ 0.05
	≥ 3	12	47.8	6	21.4	≥ 0.05

In addition, a significant difference was found between the groups in relation to the number of mother's chronic diseases. Although, no significant differences seemed to be found between the groups ($p \ge 0.05$), however, stratification of the parameter by the number of chronic diseases, namely ≤ 1 and ≥ 2 (Figure 1), showed a significant correlation between this value and the risk of cardiac arrhythmias and conduction disorders. It was as follows: fewer $(0-1; \le 1)$ chronic diseases were

characteristic of mothers of the control group children and were registered in 53.5% of them, while in the main group, the proportion of such mothers was 5 times less (10.7%; $p \le 0.001$). Significant (≥ 2) mother's morbidity was a risk factor for the studied pathology, as the proportion of mothers with ≥ 2 diseases equaled 89.3% in the main group, while in the control group, this parameter was reported 1.9 times less often (46.5%; $p \le 0.001$).



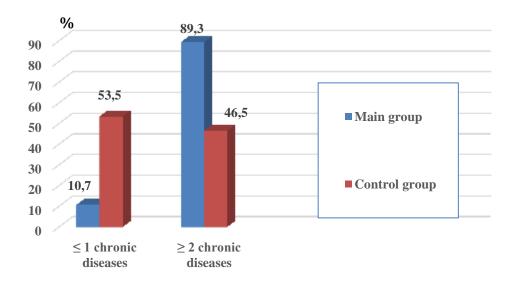


Figure 1 – Distribution of the patients in groups according to the number of mother's chronic diseases

Regarding other parameters of genetic burden, no significant difference was found between the groups (p \geq 0.05). At the same time, for most parameters (except for gastrointestinal diseases), a trend was observed indicating a greater genetic burden in the main group children.

With regard to paternal inheritance, a significant difference was observed between the groups (Table 2) regarding the specific genetic burden, i.e. cardiovascular diseases. They were observed in 42.9% of fathers in the main group and 2 times less often (21.4%; $p \le 0.05$) in the control group. No other significant differences were found ($p \ge 0.05$).

Table 2 – Paternally inherited genetic burden

Parameter	Parameter option	Group I		Group II		n
		n	%	n	%	р
Cardiovascular diseases	present	12	42.9	6	21.4	≤ 0.05
	absent	16	57	22	78.6	≤ 0.05
Gastrointestinal diseases	present	10	35.7	9	32.1	≥ 0.05
	absent	18	64.3	19	67.9	≥ 0.05
Endocrine diseases	present	5	17.9	3	10.7	≥ 0.05
	absent	23	82.1	25	89.3	≥ 0.05
Allergic manifestations	present	3	10.7	5	17.9	≥ 0.05
	absent	25	89.3	23	82.1	≥ 0.05
Respiratory diseases	present	3	10.7	4	14.3	≥ 0.05
	absent	25	89.3	24	85.7	≥ 0.05
Obesity	present	8	28.6	9	32.1	≥ 0.05
	absent	20	71.4	19	67.9	≥ 0.05
Urinary system diseases	present	4	14.3	3	10.7	≥ 0.05
	absent	24	85.7	25	89.3	≥ 0.05
Number of chronic diseases	0	2	7.1	4	14.3	≥ 0.05
	1	7	25	13	44.6	≥ 0.05
	2	14	50	10	35.7	≥ 0.05
	≥ 3	5	7.9	1	3.4	≥ 0.05



However, stratification of the parameter by the number of chronic diseases also revealed a statistically significant correlation between this factor and investigated pathology (Figure 2), i.e. fewer $(0-1; \leq 1)$ chronic diseases were 1.8 times more common in the control group vs. the main

group (58.9% and 32.1%, respectively; $p \le 0.05$), and a higher incidence (≥ 2) was characteristic of fathers of the main group patients (67.9%), while it was significantly lower (41.1%; $p \le 0.05$) in the control group.

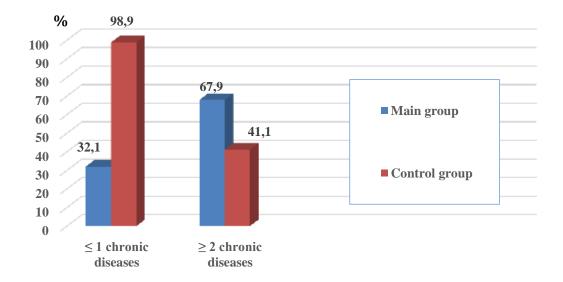


Figure 2 – Distribution of the patients in groups according to the number of father's chronic diseases

Analysis of perinatal history data in the groups revealed a significant difference for some parameters (Table 3). Thus, gravida 1 para 1 and gravida 2 para 2 mothers were significantly more common among those of patients in the control group (85.8% and 62.5%, respectively; $p \le 0.05$), while gravida 3 para 3 and more was typical for mothers of patients in the main group and were observed in 37.5% of them, while in the control group, this value was 2.6 times lower (14.2%; $p \le 0.05$).

As for the parity, the first childbirth was reported in 64.3% of mothers in the main group and in 28.6% of mothers (2.2 times less often) in the control group (p ≤ 0.05); while multipara mothers were characteristic of the control group children (71.4%), which was 2 times more often than in the main group (35.7%; p ≤ 0.05).

The risk of arrhythmia and conduction disorders also depends on the course of pregnancy. The risk factors are threatened miscarriage and toxemia in the first half of pregnancy. Thus, threatened miscarriage was reported in 46.4% of mothers of the main group children and was observed 2.2 times less often (21.4%; $p \le 0.05$) in the control group. Toxemia in the first half of pregnancy was diagnosed in 50% of

mothers of children in the main group and 2 times less often (in 25%; $p \le 0.05$) – in the control group.

Regarding toxemia in the second half of pregnancy, it was more frequent among mothers of the main group children (50% and 25%, respectively). However, for this parameter, the difference was of no statistical significance ($p \ge 0.05$).

A similar situation was observed for preeclampsia, which was reported in 28.6% of mothers of the main group patients and 2 times less often (14.3%) — in the control group. However, these differences were only regarded as trends, since they did not have statistical significance ($p \ge 0.05$).

A physiological course of childbirth played an important role in risk determination for arrhythmia and conduction disorders. Complicated childbirth was observed in 60.7% of mothers in the main group and 1.9 times less often (32.9%; $p \le 0.05$) – in the control group.

The proportion of children with central nervous system (CNS) damage in the studied groups did not differ significantly ($p \ge 0.05$).

Such parameter as birthweight revealed a controversial influence on the development of this pathology. At the same time, relatively low (up to



Parameter Group I **Group II** Parameter p option % % n 85.8 1 - 216 62.5 24 ≤ 0.05 Gravidity ≥ 3 12 37.5 4 14.2 ≤ 0.05 24 complicated 16 62.5 85.8 ≤ 0.05 Pregnancy course uncomplicated 12 37.5 4 14.2 ≤ 0.05 18 64.3 8 28.6 ≤ 0.05 Parity ≥ 2 10 35.7 20 71.4 ≤ 0.05 13 46.4 21.4 ≤ 0.05 present 6 Threatened miscarriage 22 15 53.6 78.6 ≤ 0.05 absent 14 50.0 7 25.0 ≤ 0.05 present Toxemia in the 1st half of pregnancy 14 50.0 75.0 ≤ 0.05 absent 21 15 53.6 9 32.1 ≥ 0.05 present Toxemia in the 2nd half of pregnancy 13 19 absent 46.4 67.9 ≥ 0.05 28.6 14.3 ≥ 0.05 present 8 Preeclampsia 20 71.4 24 85.7 ≥ 0.05 absent present 14 50.0 8 28.6 ≥ 0.05 Birth asphyxia 50.0 14 20 absent 71.4 ≥ 0.05 7 25.0 8 28.6 present ≥ 0.05 Newborn brain damage 21 20 71.4 absent 75.0 ≥ 0.05 17 60.7 9 32.1 ≤ 0.05 present Labor complications 11 39.3 19 67.9 ≤ 0.05 absent 9 ≤ 3000 32.1 3 10.7 ≤ 0.05 3001-3999 14 50.0 25 89.3 ≤ 0.001 Bodyweight at birth, grams

> 4000

5

17.9

Table 3 – Distribution of patients in groups according to perinatal history

3000 g) birthweight and fetal macrosomia (\geq 4000) acted as risk factors. Thus, the proportion of patients with a bodyweight of up to 3000 g was 32.1% in the main group, and 3 times less (10.7%; p \leq 0.05) – in the control group. The bodyweight of \geq 4000 g (large fetus) was a specific feature of patients in the main group, as it was reported exclusively among them (17.9%) and was not observed in the control group (0%, p \leq 0.001).

As for the reference values of bodyweight (3001–3999 g), they were found in the majority (89.8%) of patients in the control group, and were significantly less common (in 50.0%; $p \le 0.001$) in the main group.

Discussion

Analysis of the scientific literature showed that the genetic burden of cardiovascular diseases and the number of chronic diseases, both maternal and paternal, played an important role in the development of arrhythmias and conduction disorders in children. The most common perinatal risk factors for this pathology

included threatened miscarriage; toxemia; multigravida and multipara status; complicated delivery; relatively low (up to 3000 g) birthweight and fetal macrosomia (≥ 4000 g). According to scientific data, in contrast to the results of our study, children born to primigravida women were significantly more likely to develop arrhythmias; however, these data made no reckoning of whether it was an isolated arrhythmia or arrhythmia in combination with GER [9, 10, 11, 12, 13].

0

< 0.001

No data have been found on the influence of hereditary and perinatal factors on the occurrence of arrhythmias and cardiac conduction disorders in combination with concomitant gastroesophageal reflux in children.

The practical significance of this study is to develop criteria for early diagnosis and differential diagnosis of arrhythmias and cardiac conduction disorders in combination with concomitant gastroesophageal reflux vs. isolated variants of this pathology and digestive diseases accompanied by GER. These criteria will reduce



the prevalence of these pathologies; severity of complications; course severity and chronicity

Conclusions/Висновки

It was revealed that the maternal and paternal genetic burden of cardiovascular diseases and the number of chronic diseases in parents were statistically significant hereditary risk factors for the development of arrhythmias and conduction disorders in children.

frequency; risk of sudden death characteristic of arrhythmias.

It was found that statistically significant perinatal predictors of arrhythmias and conduction disorders in children with GER included threatened miscarriage; toxemia; multigravida and multipara status; complicated delivery; relatively low (up to 3000 g) birthweight and fetal macrosomia (≥ 4000 g).

Prospects for future research/Перспективи подальших досліджень

Study limitations: a small sample of patients participating in the study. A study involving a large sample of patients should be considered.

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(received 17.10.2021, published online 29.12.2021)

(одержано 17.10.2021, опубліковано 29.12.2021)



Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

Acknowledgements/Подяка

We are grateful to the patients who participated in the study, as well as to the specialists who made a significant contribution to the instrumental examination of patients.

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