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GENETIC AND ENVIRONMENTAL COMPONENTS IN THE PATHOGENESIS OF DYSMETABOLIC NEPHROPATHY WITH OXALATE-CALCIUM CRYSTALLURIA

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Summary

Introduction. In recent years, the prevalence of dysmetabolic nephropathies (DN) in children has been increasing, constituting a significant portion of the overall structure of kidney diseases in this age group.
Aim. To elucidate the role of genetic and epigenetic components in the pathogenesis of dysmetabolic nephropathy with oxalate-calcium crystalluria in children using the methods of G. Edwards and D. Falconer.
Materials and methods. A genealogical history was collected for 108 children aged 6 to 18 years with dysmetabolic nephropathy and 65 healthy children from the Ivano-Frankivsk region. Data were collected on 1076 relatives of affected children of I-II-III degrees of relatedness and 676 relatives of healthy children. Calculation of the contribution of genetic and environmental factors to the occurrence of multifactorial diseases in children was carried out using the model proposed by G. Edwards and G. Smith, and the heritability coefficient for susceptibility to these diseases was calculated using D. Falconer's model.
Results and discussion. In the pathogenesis of dysmetabolic nephropathy in children, the genetic component plays a significant role, being 2-3 times greater than in the general population. The heritability coefficient for susceptibility to dysmetabolic nephropathy is very high: for first-degree relatives of affected children – 24 %, for second-degree relatives – 20.9 %, and for third-degree relatives, it does not differ from the population average – 3.6 %.
Conclusions. 1. If a family has a child with dysmetabolic nephropathy or a relative with metabolic pathology, the risk of dysmetabolic nephropathy in the second child is higher according to the G. Edward's and G. Smith's models is very high – 36.76 % and 48.81 %. 2. For relatives of sick children of the first degree of consanguinity, the inheritance rate of predisposition to dysmetabolic nephropathy is very high – 24 % and 22 %, respectively, in the observation groups and does not depend on the variant of the course of dysmetabolic nephropathy, nor on who is sick – parents or siblings. 3. The risk of having dysmetabolic nephropathy for relatives of the second degree of consanguinity of children with dysmetabolic nephropathy is also quite high – 20.9 %. For relatives of the third degree – 3.6 %.

Keywords: **dysmetabolic nephropathy, children, genealogical history, G. Edwards model, D. Falconer model**

INTRODUCTION

In recent years, the prevalence of dysmetabolic nephropathies in children has been increasing, representing a significant portion of kidney diseases in this age group [1-3].

As part of the research conducted at the State Institution «Institute of Hereditary Pathology of the NAMS of Ukraine» by an expeditionary team of institute staff, physicians of various specialties, and a doctoral candidate, 108 children aged 6 to 18 years were examined

in the Ivano-Frankivsk region. Through the study of their medical history, medical records, and examination by various specialists (pediatricians, nephrologists, gastroenterologists, endocrinologists, immunologists), including the use of ultrasound diagnostics (USG) of internal organs, these children were diagnosed with dysmetabolic nephropathy (DN) [4-7].

Among the examined children, two groups were formed: those with dysmetabolic nephropathy and a history of secondary urinary tract infections [8-9]. Group I included 52 individuals in whom dysmetabolic nephropathy had complicated at some stage due to the superimposition of inflammatory processes in the kidneys and urinary tract – complicated DN (I-CDN). Group II consisted of 56 children with an uncomplicated course of DN (II-DN), in whom the diagnosis of dysmetabolic nephropathy was confirmed by genealogical history and specific ultrasound signs [10].

AIM

To determine the role of genetic and epigenetic components in the pathogenesis of dysmetabolic nephropathy with oxalate-calcium crystalluria in children using the methods of G. Edwards and D. Falconer.

MATERIALS AND METHODS

The assessment of the proportion of genetic and environmental factors in the pathogenesis of multifactorial diseases was conducted using the model proposed by G. Edwards and G. Smith. The calculation of the heritability coefficient of susceptibility to multifactorial diseases was performed using D. Falconer's model [6].

To clarify the significance of genetic factors in the pathogenesis of dysmetabolic nephropathy and the severity of its course in children, genealogical data from 108 families were studied. Data were collected for 1076 relatives of the first, second, and third degrees of kinship. For comparison of genealogical data of children with dysmetabolic nephropathy (DN) with data from healthy children in the control group, genealogical data were collected from 40 families with healthy children, forming a general population control group, and data were collected for 676 relatives.

Analysis of the Obtained Data: A family history burdened with kidney pathology was noted in 79 (73.15 %) of those examined: 41 children in Group I (78.85 %) and 35 children in Group II (62.5 %). This indicates the significant role of genetic factors in the pathogenesis of dysmetabolic nephropathy in children.

To assess the genealogical data, the number of relatives of each degree of kinship with metabolic pathologies, which are a further development of dysmetabolic nephropathy in adulthood (such as urolithiasis, cholelithiasis, gout), was analyzed in the families of children with DN and in the families of healthy children in the control group (table 1).

Table 1

Frequency of metabolic pathologies among relatives of the first, second, and third degrees of kinship of children with dysmetabolic nephropathy and healthy children

Type of relatives, degree of relationship	Number of parents in children with metabolic nephropathy:								
	I-CDN, n = 52			II – DN, n = 56			III – Healthy-Control, n = 65		
	total	X sick	%	total	sick	%	total	sick	%
I degree total	104	19	18,26*	156	24	15,38*	101	4	3,96
including parents	66	12	18,18*	102	15	14,71*	80	3	3,75
including siblings	38	7	18,42*,#	54	9	16,66*	21	1	4,76
II degree	139	9	6,47*	115	7	6,09*	564	16	2,83
III degree	391	9	2,30*	171	4	2,34*	111	1	0,90
Total	634	41	6,47*	442	35	7,92*	676	21	3,11

Notes: * – likely difference in the indicator between data of children with metabolic nephropathy and a healthy control group; $p<0.05$
– likely difference in the indicator between two groups of children with metabolic nephropathy; $p_1<0.01$

The provided data convincingly demonstrate a high frequency of metabolic pathology among first-degree relatives of children with metabolic nephropathy.

Yes, the frequency of metabolic pathologies among first-degree relatives of children with dysmetabolic nephropathy (DN) in both observation groups was approximately the same (18.26 % and 15.38 %), which was roughly 5 times higher than the corresponding frequency in the relatives of children in the control group (3.96 %). In siblings of children with DN, the frequency of metabolic pathologies was high, especially in children with a complicated course of DN, reaching 18.42 % compared to 16.66 % in the siblings of children in Group II and 4.76 % in the control group (table 1). This fact suggests that the genetic burden of metabolic pathology plays a significant role in the genesis of dysmetabolic nephropathy in children. It develops more rapidly in those children with a heavily burdened genealogical history of metabolic pathology, especially if parents or full siblings are affected (table 1), making these children a high-risk group for developing dysmetabolic nephropathy.

From second-degree relatives, the genealogical history was also significantly more burdened by metabolic

pathology, approximately four times higher in children of Group I (6.47 %) and Group II (6.09 %) compared to the control group (2.83 %).

The genealogical history of children with DN was twice as heavily burdened for third-degree relatives, with 2.30 % and 2.34 % in the two groups, compared to the relatives of children in the control group, which had a rate of 0.90 %.

The analysis of disease incidence among siblings, both affected by dysmetabolic nephropathy and healthy probands, showed that 18.42 % of siblings of children with a complicated course of DN and 16.66 % of siblings of children with uncomplicated DN were also diagnosed with DN, while in the control group, there was only 1 affected sibling, accounting for 4.76 % (table 2).

Table 2

Ratio of healthy and dysmetabolic nephropathy-affected siblings in the examined children's groups

Groups of children	Number of families with 2 and > children	Siblings			
		Healthy		Sick	
	n	n	%	n	%
I-CDN, $n = 52$	38	31	81,58*	7	18,42*
II – DN, $n = 56$	54	45	83,34*	9	16,66*
III – Healthy-Control, $n = 65$	21	20	95,24	1	4,76

Notes: * – Likely difference in the indicator between children with dysmetabolic nephropathy and the healthy control group; $p < 0.05$; # – Likely difference in the indicator between the two groups of children with dysmetabolic nephropathy; $p_1 < 0.01$.

In other words, the risk of developing dysmetabolic nephropathy for full siblings of children with DN increases by 3.7 to 3.5 times compared to the risk for siblings of healthy children.

Therefore, the analysis of the genealogical history of children with DN and the control group showed a high risk of developing dysmetabolic nephropathy in children whose relatives had metabolic pathologies, especially if they were first-degree relatives, including full siblings.

The calculation of the proportion of genetic and environmental factors in the occurrence of multifactorial diseases in children, including dysmetabolic nephropathy [5], was carried out using the model proposed by G. Edwards and G. Smith, utilizing information about the population frequency of this condition: if the frequency of the pathology in the population is denoted as «p,» then the frequency of affected individuals among relatives (risk of developing the disease) according to G. Edwards and G. Smith's model is determined by the equation = $\sqrt{p}$ [3].

It should be noted that a specific genetic risk of up to 5.0 % is considered low, from 5.0 % to 10.0 % is considered mild, from 10.0 % to 20.0 % is considered moderate, and above 20.0 % is considered high [7].

According to our data, the population frequency of dysmetabolic nephropathy of multifactorial origin is 3.11 %, which is denoted as p = 0.031. Therefore, the risk of developing dysmetabolic nephropathy in a child from a family with one healthy child is accordingly calculated as 0.176 or 17.6 %, which is considered moderate.

In families of children with a complicated course of DN, 6.47 % of relatives had metabolic pathologies, while in families of children with an uncomplicated course of DN, 7.92 % of relatives had metabolic pathologies (table 1).

If the discrepancy between the expected and observed frequencies of dysmetabolic nephropathy can be explained by the influence of environmental factors, then the heritability fraction in the development of DN in families of children with a complicated course of DN according to the G. Edwards model would be = (6.47 * 100) / 17.6 = 36.76 %, and in the group of children with an uncomplicated course of DN = (8.59 * 100) / 17.6 = 48.81 %. Therefore, in the pathogenesis of dysmetabolic nephropathy according to the G. Edwards and G. Smith model, the genetic component plays a very important role (36.76 % and 48.81 % in the observation groups, respectively), with a significant impact of a burdened genealogical history of metabolic pathology. These calculations strongly indicate the crucial role of the genetic component in the pathogenesis of dysmetabolic nephropathy.

Environmental factors play a significant role in the pathogenesis of dysmetabolic nephropathy, according to calculations using the G. Edward's and G. Smith's methods, accounting for no less than 63.24 % and 51.18 %, respectively. Environmental factors can include diet, fluid intake, living conditions, and the impact of xenobiotics on the child's body. Therefore, with appropriate correction of the environmental component in children from families with diagnosed metabolic pathology, it is possible to significantly prevent the development of the disease in the child.

Therefore, the calculation of the genetic and environmental components in the pathogenesis of dysmetabolic nephropathy using the G. Edward's and G. Smith's model allows us to conclude that the genetic component plays a substantial role, approximately 2-3 times greater than the population average, regardless of whether the course of dysmetabolic nephropathy is complicated by inflammation of the urinary tract organs or not. In the presence of a child with dysmetabolic nephropathy in the family or a relative with metabolic pathology, the risk of developing DN in another child

according to the G. Edward's and G. Smith's model is very high, ranging from 48.81 % to 36.76 %. This risk increases by 3.5 times if a full sibling is affected by dysmetabolic nephropathy.

The heritability coefficient of susceptibility to multifactorial pathology, including dysmetabolic nephropathy, is commonly calculated using the method proposed by D. Falconer [4].

According to this model, the heritability (h^2) of children's predisposition to the disease is determined by the regression coefficient (b) of children on the proband.

The regression coefficient is calculated using the formula: $b = (X_{control\ group.} - X_{groups})/a$,

$X_{control\ group}$ – average susceptibility to illness in the control group of healthy children,

X_{groups} – average susceptibility to illness in groups of parents of sick children,

a – deviation corresponding to the frequency of affected relatives (q).

Value $X_{control\ group}$, $X_{groups.}$ and a is obtained from the provided tables D. Falconer [4].

The relationship between regression and the coefficient of heritability of susceptibility to illness is expressed by the formula:

$$h^2 = b/r,$$

Where r is the degree of relatedness.

For first-degree relatives, the coefficient of relatedness according to the D. Falconer model is 1/2. For second-degree relatives, it is 1/4, and for third-degree relatives, it is 1/8.

The calculation of the inheritance coefficient for predisposition to dysmetabolic nephropathy according to the D. Falconer model for various types of its course is presented in table 3.

Table 3

Estimation of the inheritance coefficient of predisposition to dysmetabolic nephropathy in families of probands with different types of its course

Distribution of Relatives by Degree of Kinship	A, number of patients	*N*, total number	*q* frequency	Falconer's				
				1 – *q*	x	a	b	h^2
Parents of the First Degree of Children with CDN, *n* =52								
Total	19	104	0,18	0,82	2,911	3,201	0,12	24,0 %
including parents	12	66	0,18	0,82	2,911	3,201	0,12	24,0 %
including siblings	7	38	0,18	0,82	2,911	3,201	0,12	24,0 %
Parents of the First Degree of Children with DN, *n* = 56								
Total	24	156	0,15	0,85	2,968	0,82	0,11	22,0 %
including parents	15	102	0,15	0,85	2,968	0,82	0,11	22,0 %
including siblings	9	54	0,17	0,83	2,929	0,82	0,11	22,0 %
Parents of the First Degree of Kinship of Children in the Control Group, *n* = 65								
Total	4	101	0,04	0,96	3,353	3,613		
including parents	3	80	0,04	0,96	3,353	3,613		
including siblings	1	21	0,05	0,95	3,291	3,554		
Relatives of the II Degree of Kinship								
I-CDN	9	139	0,06	0,94	3,239	3,507	0,209	20,9 %
II – DN	7	115	0,06	0,94	3,239	3,507	0,209	20,9 %
III – Healthy-Control	16	564	0,03	0,97	3,432	3,687		
Relatives of the III Degree of Kinship								
I-CDN	9	391	0,02	0,98	3,540	3,790	0,45	3,6 %
II – DN	4	171	0,02	0,98	3,540	3,790	0,045	3,6 %
III – Healthy-Control	1	111	0,01	0,99	3,719	3,960		

The calculation of the heritability coefficient of susceptibility to dysmetabolic nephropathy in relatives of children with different courses of the disease showed that for first-degree relatives of affected children, the risk of developing DN was very high, at 24 % and 22 %, respectively, in both observation groups. This risk was independent of the variant of DN progression and whether the parents or siblings were affected. This is consistent with the calculations of the genetic component's role in the genesis of nephropathies in full siblings using the G. Edward's and G. Smith's model (table 3).

The heritability coefficient of susceptibility to dysmetabolic nephropathy for second-degree relatives of affected children was also relatively high at 20.9 %, while for third-degree relatives of children with DN, it did not differ from the population average, which is 3.6 %.

CONCLUSIONS

1. In the presence of a child with dysmetabolic nephropathy or a relative with metabolic pathology in the family, the risk of developing dysmetabolic nephropathy in another child, according to the G. Edward's and G. Smith's model, is very high – 36.76 % and 48.81 %, respectively. This risk becomes 3.5 times higher if a first-degree sibling has metabolic nephropathy. Thus, the genetic component in the pathogenesis of dysmetabolic nephropathy in children plays a significant role, 2-3 times greater than in the general population.

2. For parents of sick children in the first degree of kinship, the coefficient of predisposition inheritance to dysmetabolic nephropathy is very high – 24 % and 22 % according to the observation groups, and it does not depend on the variant of the course of dysmetabolic nephropathy or who is affected – parents or siblings.

3. The risk of having dysmetabolic nephropathy for second-degree relatives of children with dysmetabolic nephropathy is also quite high – 20.9 %. For third-degree relatives of children with dysmetabolic nephropathy, the risk of its occurrence is not different from the population average – 3.6 %.

Future research perspectives. Further studies of epigenetic factors in the pathogenesis of dysmetabolic nephropathy are of great importance for understanding the mechanisms of development of this disease and its complications. Studying the influence of various factors will allow developing effective methods of prevention and treatment, which will help improve the quality of life of children with dysmetabolic nephropathy.

FUNDING AND CONFLICT OF INTEREST

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COMPLIANCE WITH ETHICAL REQUIREMENTS

The scope and methods of the study do not contradict the basic principles of the Declaration of Helsinki for Biomedical Research (1974), adapted at the 41st International Assembly in Hong Kong (September 1989), in which human beings are the subject of research. The study was conducted in compliance with such basic principles as respect for the individual, patient information, and risk-benefit assessment. Compliance with bioethical requirements in scientific research meets the requirements of the Ethics Committee of Ivano-Frankivsk National Medical University.

AUTHOR'S CONTRIBUTION TO THE ARTICLE

Nadia R. Aib – author of the idea, material selection and analysis, Natalia S. Lukyanenko – substantiation of relevance, translation and editing of the text, Hanna S. Chaikovska – statistical processing of data, Andriy B. Volosianko – literature review on this issue, preparation of primary research material.

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Резюме

ГЕНЕТИЧНА ТА СЕРЕДОВИЩНА КОМПОНЕНТИ У ПАТОГЕНЕЗІ ДИЗМЕТАБОЛІЧНОЇ НЕФРОПАТІЇ З ОКСАЛАТНО-КАЛЬЦІЄВОЮ КРИСТАЛУРІЄЮ

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Вступ. В останні роки поширеність дисметаболічних нефропатій у дітей зростає, що становить значну частку в загальній структурі ниркових захворювань цього віку [2].
Мета. З'ясувати роль генетичної та епігенетичної компонентів у патогенезі дисметаболічної нефропатії з оксалатно-кальцієвою критсталурією у дітей за методами Г. Едвардса і Д. Фальконера.
Матеріали та методи. В родинах 108 дітей віком від 6-ти до 18 років з дизметаболічною нефропатією та 65 здорових дітей з Івано-Франківської області зібраний генеалогічний анамнез. Дані зібрано про 1076 родичів хворих дітей I-II-III ступеню спорідненості та 676 родичів здорових дітей. Підрахунок частки генетичних та середовищних факторів у виникненні в дітей захворювань мультифакторного генезу проводили за моделлю, запропонованою Г. Едвардсом та Г. Смітом, а коефіцієнт успадкування схильності до цих захворювань за моделлю Д. Фальконера.
Результати та обговорення. У патогенезі дизметаболічної нефропатії у дітей генетична компонента відіграє суттєву, в 2-3 більшу за загально популяційну, роль. Коефіцієнт успадкування схильності до дисметаболічної нефропатії є дуже високий: для родичів I ступеню спорідненості хворих дітей – 24 %, для родичів II ступеню спорідненості – 20,9 %, а для родичів III ст. спорідненості не відрізняється від середньопопуляційного – 3,6 %.
Висновки. 1. Якщо в сім'ї є дитина з дисметаболічною нефропатією або родич з метаболічною патологією, ризик розвитку дисметаболічної нефропатії у другої дитини за моделями G. Edward і G. Smith є дуже високим – 36,76 % і 48,81 %. 2. Для родичів хворих дітей першого ступеня спорідненості частота успадкування схильності до дисметаболічної нефропатії дуже висока – 24 % і 22 % відповідно в групах спостереження і не залежить ні від варіанту перебігу дисметаболічної нефропатії, ні від того, хто хворий – батьки чи брати і сестри. 3. Ризик мати дисметаболічну нефропатію для родичів другого ступеня спорідненості дітей з дисметаболічною нефропатією також досить високий – 20,9 %. Для родичів третього ступеня – 3,6 %.

Ключові слова: **дисметаболічна нефропатія, діти, генеалогічний анамнез, модель Г. Едвардса, модель Д. Фальконера**