UDC 616.61-053.2:575:576.5

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The role of epigenetic factors in the pathogenesis of dysmetabolic nephropathy with calcium oxalate crystalluria in children

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Modern Pediatrics. Ukraine. (2024). 6(142): 27-34. doi: 10.15574/SP.2024.6(142).2734

For citation: Aib NR, Hnateyko OZ, Lukyanenko NS, Volosyanko AB. (2024). The role of epigenetic factors in the pathogenesis of dysmetabolic nephropathy with calcium oxalate crystalluria in children. Modern Pediatrics. Ukraine. 6(142): 27-34. doi: 10.15574/SP.2024.6(142).2734.

The prevalence of dysmetabolic nephropathies in children is increasing from year to year, representing a significant problem in the overall structure of kidney diseases in pediatric age. Despite numerous studies dedicated to the issue of dysmetabolic nephropathies in children, the role of epigenetic factors in the pathogenesis of dysmetabolic nephropathy with calcium oxalate crystalluria remains insufficiently explored.

Aim — to identify the leading epigenetic factors in the pathogenesis of dysmetabolic nephropathy with calcium oxalate crystalluria in children.

Materials and methods. The data from the medical histories and outpatient records of 173 children were studied. Each child was additionally examined by narrow specialists of different profiles. Three groups were formed from the examined children: Group I — children with a complicated course of dysmetabolic nephropathy and a history of inflammatory processes in the urinary system (52 children), Group II — children with dysmetabolic nephropathy with persistent crystalluria (56 children) and the Control group, which included 65 healthy children.

Results. The most significant prenatal epigenetic factors are the threat of early miscarriage, gestosis of the first and second halves of pregnancy, maternal anemia during pregnancy, parental alcohol and tobacco use, mother's work on computer during pregnancy, presence of maternal chronic diseases, parental exposure to industrial dust and noise, and heavy physical work of mother leading to fetal hypoxia.

Conclusion. The most significant postnatal epigenetic factors influencing children's susceptibility to a more severe course of dysmetabolic nephropathy included low birth weight, early artificial feeding, frequent acute respiratory infections, atopic diathesis, and physiological jaundice in the first year of life, as well as the presence of concomitant diseases such as chronic tonsillitis, dental caries, frequent acute respiratory infections, chronic gastritis, atopy, and chronic cholecystitis later in life.

The study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of these institutions. The informed consent of the children's parents was obtained for the research.

No conflict of interests was declared by the authors.

Keywords: life history, dysmetabolic nephropathy, children, epigenetic factors, pathogenesis.

Роль епігенетичних факторів у патогенезі дисметаболічної нефропатії з оксалатно-кальцієвою кристалурією в дітей

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Поширеність дисметаболічних нефропатій у дітей зростає з року в рік, становлячи значну проблему в загальній структурі захворювань нирок у дитячому віці. Попри численні дослідження, присвячені проблемі дисметаболічних нефропатій у дітей, роль епігенетичних факторів у патогенезі дисметаболічної нефропатії з оксалатно-кальцієвою кристалурією залишається недостатньо вивченою.

Мета: визначити провідні епігенетичні фактори в патогенезі дисметаболічної нефропатії з оксалатно-кальцієвою кристалурією в дітей.

Матеріали та методи. Вивчено дані історій хвороби та амбулаторних карт 173 дітей. Кожна дитина була додатково оглянута вузькопрофільними спеціалістами різного профілю. З обстежених дітей було сформовано три групи: I група — діти з ускладненим перебігом дисметаболічної нефропатії, наявністю в анамнезі запальних процесів в органах сечовидільної системи в минулому (52 дитини), II група — діти з дисметаболічною нефропатією зі стійкою кристалурією (56 дітей) та контрольна група, до якої увійшло 65 здорових дітей.

Результати. Найбільш значущими пренатальними епігенетичними факторами були загроза переривання вагітності на ранніх термінах, гестози першої та другої половини вагітності, анемія матері під час вагітності, вживання батьками алкоголю та тютюну, робота матері за комп'ютером під час вагітності, наявність у матері хронічних захворювань, вплив виробничого пилу та шуму, а також важка фізична праця матері, що призводить до гіпоксії плода.

Висновок. Найбільш значущими постнатальними епігенетичними факторами, що впливають на схильність дітей до тяжчого перебігу дисметаболічної нефропатії, були низька маса тіла при народженні, раннє штучне вигодовування, часті гострі респіраторні інфекції, атопічний діатез і фізіологічна жовтяниця на першому році життя, а також наявність супутніх захворювань, таких як хронічний тонзиліт, карієс зубів, часті гострі респіраторні інфекції, хронічний гастрит, атопія і хронічний холецистит у подальшому житті.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: анамнез життя, дисметаболічна нефропатія, діти, епігенетичні фактори, патогенез.

Introduction

Dysmetabolic (metabolic) nephropathies (DN) are a group of diseases with various etiologies and pathogenesis, characterized by an aseptic tubulointerstitial process in the kidneys due to metabolic disorders and capable of leading to the adhesion of crystals in the renal collecting system, forming concrements, the development of secondary urinary tract infections, and disturbances in urodynamics [6].

Genetic factors play an important role in predisposition to the development of various diseases, including DN. There may be certain genes or genetic variants that increase the risk of developing this condition. However, epigenetic factors also play a significant role in the pathogenesis of multifactorial diseases [1].

Epigenetic factors encompass changes in genes that do not affect the DNA sequence but can influence how genes are turned on or off. This can result from external factors such as diet, environment, and other factors. Epigenetic changes can affect the functioning of the kidneys and their ability to handle metabolic tasks, thereby contributing to the development of DN.

Overall, it is the interaction between genetic and epigenetic factors that plays a pivotal role in determining susceptibility to DN and its subsequent development [1].

There is no doubt that in such fundamental, overarching biological processes as the development of an individual organism, evolution of human pathology, mechanisms of gene expression, and disease onset, epigenetic hereditary variability plays a significant role [3].

Today, many studies provide evidence for one of the leading epigenetic hypotheses, which suggests that external inducing factors can influence gene expression. The research results of R. Müller and M. Kenney suggest that environmental factors can induce stable changes in the epigenetic states of the organism, providing a mechanism by which environmental factors can lead to long-term biological effects [5].

The aim of the study is to identify the leading epigenetic factors in the pathogenesis of DN with calcium oxalate crystalluria in children.

Materials and methods of the study

To investigate the role of epigenetic factors in the pathogenesis of DN and its complications with urinary tract infections (UTIs) in examined children, the data from medical history and outpatient medical records (Form 112/o) of 108 children with DN and 65 outpatient records of healthy children in the Control group were analyzed. Each child in the study underwent additional examinations by various specialized doctors (pediatrician, otolaryngologist, gastroenterologist, neurologist, ophthalmologist). The obtained data were systematized in a journal, where, in each case, the child's date of birth, gender, birth weight, feeding pattern, time of teething, presence of pregnancy complications, blood group (AB0 system), Rh factor, frequency, and severity of concomitant diseases were recorded. Among the examined children, studied groups were formed — those with complicated DN, a history of UTI in the past (Group I — 52 children), those with DN with persistent crystalluria (Group II — 56 children), and the Control group — 65 healthy children.

The statistical processing of clinical and laboratory parameters was carried out according to the generally accepted methodology. To check the normality of the distribution, the Shapiro–Wilk test was calculated. Quantitative data with a normal distribution were presented in the form of the arithmetic mean and its error (M±m). In the course of processing, the mean value of M, the standard error of the arithmetic mean m, and the value of the Student's t coefficient were calculated for each set. The reliability of the results obtained by the values of the Student's coefficient t and the number of observations n in each set was assessed according to the tables «The value of the normal integral of probabilities within ± t» and «The area of the probability curve within ± t for a small population size». For each comparison, the probability (p) that the difference is not significant was found. The probability (p) for most sets did not exceed 0.05. The probability value of p was found in the table «Values of the normal integral of probabilities within ± t» in accordance with the value of the Student's coefficient.

The study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of these institutions. The informed consent of the children's parents was obtained for the research.

Results of the study and discussion

To analyze the possible impact of low or, conversely, excessive birth weight of a child on the pathogenesis of DN, subgroups were identified

Table 1

Birth weight of examined children with dysmetabolic nephropathy

Birth weight categories	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
Low	3	5.77*,#	0	0.00	0	0.00
Below average	8	15.38*,#	5	8.93	4	6.15
Average	39	75.00*,#	48	85.71	58	89.23
Above average	2	3.85	3	5.36	3	4.62

Notes: * — likely difference in indicators between children with different variants of the course of DN and the Control group, p<0.05; * — likely difference in indicators between children of the Groups I and II DN, p<0.05.

Table 2

Frequency of antenatal epigenetic risk factors for the development of pathology in children with dysmetabolic nephropathy

Antenatal epigenetic risk factors	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
Threat of termination of pregnancy	8	15.83*,#	5	8.93	6	9.23
Gestosis in the first half of pregnancy	28	53.85*,#	16	28.57*	10	15.38
Gestosis in the second half of pregnancy	14	26.92*,#	9	16.07*	5	7.69
Maternal anemia during pregnancy	31	59.62*,#	11	16.93*	5	7.69

Notes: * — likely difference in the indicator between children with DN and the Control group; p<0.05; # — likely difference in the indicator between studied groups; <0.01.

among children in both groups based on birth weight. A weight less than or equal to 2550 g was considered low, below average — from 2551 to 3050 g, average — from 3051 to 3950 g, and above average — from 3951 g and above [4]. The results of the analysis are presented in Table 1.

The analysis of tabular data suggests that in Group I of children with complicated DN, there was a significantly higher frequency of low birth weight, less than 2550 grams, which was observed in 5.77% of the examined children (for comparison — low birth weight was not observed in children from the Group II and the Control group at all). The birth weight below average was noted in 15.38% of children in the Group I and 8.93% in the Group II (compared to 6.15% in the Control group). The average birth weight was noted in significantly fewer children in the Group I (75.00%) compared to the Group II (85.71%) and the Control group (89.23%). However, the birth weight above average was noted in approximately the same proportion of children in all three groups (3.85% in the Group I, 5.36% in the Group II, and 4.62% in the Control group).

Therefore, there appears to be a connection between low birth weight and the subsequent development of a more complicated inflammatory course of DN in children. Thus, birth weight may serve as an epigenetic triggering factor for a more severe course of DN.

To investigate the causes that could lead to a decrease in fetal body weight, antenatal epigenetic risk factors for the development of pathology were analyzed (Table 2).

The analysis of tabular data indicates that mothers of children in the studied groups had complications during pregnancy, with the frequency of complications significantly differing from the data of mothers in the Control group (Table 2). However, the analysis of the frequency of epigenetic antenatal risk factors for the development of pathology in the obstetric history of children in different groups showed that mothers of children in the Group I suffered from anemia during pregnancy significantly more often than mothers of children in the Group II (almost three times: 59.62% versus 16.93%, compared to 7.69% in the Control group). They also had significantly more clinical manifestations of gestosis in the first half of pregnancy, nearly twice as often: 53.85% versus 28.57% of mothers in the Group II (15.38% in the Control group) (Table 2), and gestosis in the second half of pregnancy — 26.92% versus 16.07% (the Control group — 7.69%). Furthermore, mothers of children in the Group I experienced a threat of early termination of pregnancy twice as often — 15.83% versus 8.93% of mothers in the Group II, with the frequency not differing from the Control group (Table 2). Therefore, the threat of early termination of pregnancy, gestosis in the first and second halves of

Table 3

Occupational hazards in parents of children with dysmetabolic nephropathy in two groups compared to the data of healthy children

Professional harm and illnesses in parents**	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
Exposure to chemical compounds	5	9.62*	5	8,93*	2	3.08
Contact with industrial dust	11	21.15*	10	17.86*	7	10.77
Impact of industrial noise	12	23.07*,#	11	19.64*	4	6.15
Mother's work on computer	23	44.23*,#	18	32.14*	4	6.15
Impact of non-ionizing radiation	0	0.00	0	0.00	0	0.00
Impact of ultrasound	5	9.62*	4	7.14*	0	0.00
Heavy physical work of mother	12	23.07*,#	10	17.86	9	13.85
Impact of vibration	4	7.69*,#	0	0.00	0	0.00
Parental alcohol and tobacco use	38	73.07*,#	28	50.00*	16	24.62
Chronic illnesses of mother	23	44.23*,#	21	37.50*	10	15.38
Chronic illnesses of father	8	15.38*	8	14.29*	5	7.69

Notes: * — likely difference in the indicator between Groups I, II and the control group $p<0.05$; # — significant difference in the indicator between the studied groups $p<0.01$; ** — parents of one child may have multiple professional hazards, illnesses, and harmful habits.

pregnancy, and anemia during pregnancy may be predictive epigenetic factors predisposing children to the development of DN and a more severe course of the disease in the future, with a prominent role played by maternal anemia and gestosis in the first half of pregnancy. These conditions likely lead to fetal hypoxia, which becomes an epigenetic factor in the pathogenesis of DN.

To establish the role of such epigenetic factors in the formation of pathology during the antenatal period, such as parental occupational hazards and illnesses, a comparison of their frequency among the mothers of the examined children was conducted. The analysis of the frequency of various occupational hazards in the parents of the examined children is presented in Table 3.

In parents of children in the Groups I and II, the frequency of contact with occupational hazards and the incidence of chronic metabolic pathology and internal organ diseases were significantly higher than in parents of children in the Control group (Table 3). The most significant contributing epigenetic factors to the pathogenesis of DN were parental alcohol consumption and tobacco smoking (73.07% and 50.00% compared to 24.62% in the Control group), mother's work on computer (44.23% and 32.14% compared to 6.15% in the Control group), and the presence of chronic illnesses in mother (44.23% and 37.50% compared to 15.38% of mothers of children in the Control group).

The frequency of contact with industrial dust, industrial noise, and heavy physical work of mother was also significantly higher in parents of children with DN (21.15%, 23.07%, 23.07% in parents of the Group I; 17.86%, 19.64%, and 17.86% in parents of the Group II), which significantly exceeded the data in parents of the Control group — 10.77%, 6.15%, and 13.85%, respectively. It should be noted that the influence of epigenetic factors such as occupational hazards, harmful habits, and the presence of chronic pathology in the mother was significantly greater in children of the Group I (Table 3).

Thus, the teratogenic effect of occupational hazards, harmful habits, and maternal illnesses on the developing fetus is evident. These factors predisposed children to DN in general and, especially, to a complicated course of DN. In the pathogenesis of DN in children, the most significant factors were parental alcohol consumption and tobacco smoking, mother's work on the computer, the presence of chronic diseases in the mother, parental contact with industrial dust and noise, and heavy physical work of pregnant mother. It can be assumed that under these conditions, the fetus is exposed to factors that lead to intrauterine hypoxia, which becomes the main epigenetic factor in the pathogenesis of DN.

It is known that feeding a child during the first year of life plays a leading role in the formation of immunity because maternal milk contains antibodies, providing passive immune protection to the child against diseases [7]. Thus, the feeding pattern during the first year of life can serve as an epigenetic factor in the development of any pathology, including influencing the severity of DN. An analysis of the feeding pattern during the first year of life in children with DN from two study groups is presented in Table 4.

Table 4

Feeding pattern and its duration in examined children with dysmetabolic nephropathy

The duration of breastfeeding, months	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
0	18	34.62*,#	3	5.36*	1	1.54
3	17	32.69*,#	5	8.93	5	7.69
6	14	26.92*,#	35	62.5	38	58.46
12	3	5.77*	13	23.21	16	24.62
18	0	0.00*	0	0.00*	5	7.69
24	0	0.00	0	0.00	0	0.00

Notes: * — the likely difference in the indicator between the data of children with DN and the Control group p<0.05; # — the likely difference in the indicator between the studied groups; <0.01.

Table 5

Statistical significance of differences in the duration of breastfeeding between two groups of children with pyelonephritis

Epigenetic factor	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	T-tests	p	T-tests	p	T-tests	p
Duration of breastfeeding	3.619	0.005	7.589	0.005	0.859	⩽0.000

Table 6

Analysis of postnatal epigenetic risk factors for pathology development in children with varying severity of metabolic nephropathy

Non-specific risk factors	Groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
Low birth weight (2550–3000 g)	11	21.15*,#	5	8.93	4	6.15
Early artificial feeding	35	67.31*,#	8	14.28	9	13.85
Frequent respiratory tract infections (more than 5 per year)	37	71.15*,#	7	12.50	8	12.31
History of atopic dermatitis	18	34.62*,#	4	7.14*	1	1.54
Neonatal jaundice	21	40.38*,#	10	17.85*	9	13.85

Notes: * — likely difference in the indicator between children with metabolic nephropathy and the Control group p<0.05; # — likely difference in the indicator between two groups p<0.01.

In the Control group, there was only one child who was exclusively formula-forfed from birth (1.54%). At the same time, a third (34.62%) of the children in the Group I and three (5.36%) children in the Group II did not receive any breastfeeding at all. Only 3/4 of the children in the Group I (32.69%) and an equal number of children in the Group II (8.93%) and the Control group (7.69%) were breastfed for up to 3 months.

Regarding exclusive breastfeeding up to 6 months, only 26.92% of children in the Group I, 62.5% of children in the Group II, and 58.46% of children in the Control group were on natural breastfeeding. Therefore, three-quarters of the examined children in the Group I were either exclusively formula-fed or received breast milk for only the first 3 months.

There was no significant difference in the indicator of breastfeeding for more than 6 months between children in the Group II and the Control group (23.21% and 24.62%, respectively). However, only 5.77% of children in the Group I, 23.21% of children in the Group II, and 24.62% of children in the Control group received breastfeeding for more than 6 months, and the duration of breastfeeding up to 18 months was only observed in the Control group (7.69%) and was not observed in children in the Groups I and II. These data suggest the importance of natural breastfeeding in the pathogenesis of the course of DN and the development of kidney inflammation in the future. Its absence may be an epigenetic factor in the formation of a more severe course of DN in a child.

Using the Student's *t*-test, differences in the duration of breastfeeding between two groups of children with pyelonephritis were calculated, as presented in Table 5.

When comparing the duration of breastfeeding in the Groups I and II, it was found that in

Table 7

Concomitant pathology in children with varying severity of metabolic nephropathy

Diseases detected	Frequency of detected pathology (%) in the groups of children					
	I (n=52)		II (n=56)		Control (n=65)	
	n	%	n	%	n	%
Chronic tonsillitis	21	40.38*,#	12	21.43*	3	4.62
Tooth decay	18	34.62*,#	9	16.07*	0	0.00
Chronic gastritis	12	23.08*,#	6	10.71*	0	0.00
Chronic cholecystitis	6	11.54*,#	1	1.79	0	0.00
Functional disorders of the biliary tract with a hypokinetic type	12	23.08*,#	7	12.50*	3	4.62
Frequently ill child (more than 5 times a year)	37	71.15*,#	7	12.50	8	12.31
Pyelonephritis and urinary tract infections in the child's medical history	52	100.00*,#	0	0.00	0	0.00
Nocturnal enuresis	13	25.00*	18	32.14*,#	3	4.62
Hypoplasia of tooth enamel of grades I–II	14	26.92*	15	26.79*	0	0.00
Atopic dermatitis	12	23.08*,#	4	7.14*	0	0.00
Goiter of the 1st grade	8	15.38*,#	4	7.14*	2	3.08
Goiter of the 2nd grade	4	7.69*,#	0	0.00	0	0.00
CNS pathology: vegetative-vascular dystonia of the hypotonic type	7	13.46*,#	3	5.36*	1	1.54

Notes: * — likely difference in the indicator between children with dysmetabolic nephropathy and the Control group $p<0.05$; # — likely difference in the indicator between the studied groups <0.01.

children of the Group I, the average duration of breastfeeding was 3.619 months ($p\leqslant0.005$), while in children of the Group II, the average duration was 7.589 months ($p\leqslant0.005$), and in the Control group, it was 0.859 ($p\leqslant0.000$). This confirms the previous conclusion about the potential for the duration of breastfeeding to be an epigenetic factor in the development of metabolic nephropathy later in life.

It is known that, in addition to early artificial feeding, other postnatal epigenetic risk factors for the severity of any disease course may include illnesses that the child suffered from during the first year of life. The frequency of such potential postnatal epigenetic factors in children with varying severity of metabolic nephropathy was analyzed (Table 6).

The analysis of the data presented in Table 6 revealed that during the first year of life, the majority of children in the Group I (71.15%) had experienced acute respiratory infections (ARI) more than 5 times, whereas the frequency of children with frequent illnesses in the Group II was the same (12.50%) as in the Control group (12.3%). Children with DN in both groups were significantly more likely to exhibit atopic symptoms. However, in the Group I one-third (34.62%) of all examined children had such symptoms compared to 7.14% in the Group II and 1.53% in the Control group. Therefore, in the Group I, the prevalence of children with atopic symptoms during the first year of life was five times higher than in the Group II (Table 6). In the Group I 40.38% of children had neonatal physiological jaundice, while in the Group II, only 17.85% had it, and in the Control group, 13.85% of children had neonatal physiological jaundice.

Thus, low birth weight, early artificial feeding, frequent viral infections, a history of atopic dermatitis in the first year of life, and neonatal physiological jaundice can be considered significant postnatal epigenetic factors that, among other factors in the first year of life, contributed to more severe course of metabolic nephropathy with the future development of inflammatory processes in the urinary system.

It is undeniable that the presence of certain chronic conditions in a child can provoke secondary reactive disorders in internal organs and systems, thus acting as epigenetic factors that ultimately determine the quality of life and health prognosis of the patient [2]. The analysis of concomitant pathology based on the medical history data recorded in form 112/o for the examined children is presented in Table 7.

Analysis of the tabular data revealed that in the vast majority of children with a complicated course of DN, comorbid pathology was present, while in children of the Group II, comorbid pathology was also diagnosed, but the percentage of children who had it was minimal. For some nosologies (chronic cholecystitis, frequent respiratory infections, and grade II goiter), the frequency did not differ from the Control group data (Table 7).

An interesting finding was the fact that the frequency of enamel hypoplasia in teeth I–II grades was the same in children from the studied groups (26.92% and 26.79% respectively). Presumably, such a relatively high and equal frequency of tooth

enamel involvement in children, regardless of the severity of the course of DN, is related to disturbances in calcium metabolism in the pathogenesis of DN, which requires further study.

Children in the Group I significantly more often suffered from chronic bacterial and viral diseases, such as chronic tonsillitis (40.38% compared to 21.43% in the control data — 4.62%), tooth decay (34.62% compared to 16.07% in the control data — 0.00%), chronic ENT (ear, nose, throat) infections (40.38% compared to 21.43% in the control data — 4.62%), frequent respiratory infections (100.0% compared to 0.00% in the control data — 0.00%), chronic gastritis (23.08% compared to 10.71% in the control data — 0.00%), and chronic cholecystitis (11.54% compared to 1.79% in the control data — 0.00%). This may indicate the significant role of comorbid bacterial and viral pathology as epigenetic factors in the pathogenesis of DN.

Children in the Group I had significantly higher rates of atopy (23.08% compared to 7.14% in the control data — 0.00%), grade I–II goiter (15.38% compared to 7.14% in the control data — 3.08%), and vegetative-vascular dystonia of the hypokinetic type (13.46% compared to 5.36% in the control data — 1.54%). Therefore, the presence and quantity of comorbid pathology associated with DN serve as powerful epigenetic factors not only predisposing a child to DN but also influencing the severity of its course.

Thus, the analysis of prenatal epigenetic factors that played a significant role in the pathogenesis of the formation of DN and its subsequent severity in children revealed that the most significant prenatal factors were the threat of early termination of pregnancy, gestosis in the first and second halves of pregnancy, maternal anemia, parental alcohol and tobacco use, mother's work on computer during pregnancy, maternal chronic illnesses, parental exposure to industrial dust and noise, and heavy physical work of mother, leading to fetal hypoxia.

The most significant postnatal epigenetic factors influencing children's susceptibility to a more severe course of DN with inflammation of the urinary system were low birth weight, early artificial feeding, frequent respiratory infections, atopic diathesis, and physiological jaundice in the first year of life. Later in life, the presence of comorbidities such as chronic tonsillitis, tooth decay, frequent respiratory infections, chronic gastritis, atopy, and chronic cholecystitis had a significant impact on the physical development of these children, resulting in a substantial percentage of them experiencing developmental delays. These factors ultimately became significant epigenetic contributors to the pathogenesis of DN in children and its more severe course.

Conclusions

The most significant antenatal epigenetic factors, along with classical pathogenetic factors of DN, which together contributed to its development in the fetus and a more severe course in the postnatal period, were identified as follows: the threat of early termination of pregnancy, gestosis in the first and second halves of pregnancy, maternal anemia, parental alcohol and tobacco use, mother's work on computer during pregnancy, the presence of chronic maternal illnesses, parental exposure to industrial dust and noise, and heavy physical work of mother leading to fetal hypoxia.

The leading postnatal epigenetic factors that not only led to the development but also to a more severe course of DN included: low birth weight, early artificial feeding, frequent respiratory tract infections, atopic diathesis, and physiological jaundice. In later life, the presence of concomitant diseases such as chronic tonsillitis, dental caries, frequent respiratory tract infections, chronic gastritis, atopy, and chronic cholecystitis resulted in the delayed physical development of a significant number of children with a more severe course of DN.

A relatively high frequency (in every fourth child) of enamel hypoplasia of teeth was diagnosed, regardless of the severity of DN, which is associated with calcium metabolism features in the pathogenesis of this pathology.

Future research perspectives. Further studies of epigenetic factors in the pathogenesis of DN 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 of effective methods of prevention and treatment, which will help improve the quality of life of children with DN.

No conflict of interests was declared by the authors.

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Стаття надійшла до редакції 24.06.2024 р., прийнята до друку 15.10.2024 р.