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INFLUENCE OF CHOLERETIC THERAPY ON THE MICRORNA-4714-3P EXPRESSION LEVEL IN CHILDREN WITH FUNCTIONAL DISORDERS OF THE GALLBLADDER AND ODDI'S SPHINCTER

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Key words: *functional disorders of the gallbladder and Oddi's sphincter, miRNA-4714-3p expression level, choleretic therapy, ursodeoxycholic acid, children*

Ключові слова: *функціональні розлади жовчного міхура та сфінктера Oddi, рівень експресії мікроРНК-4714-3р, холеретична терапія, урсодезоксихолева кислота, діти*

Ключевые слова: *функциональные расстройства желчного пузыря и сфинктера Oddi, уровень экспрессии микроРНК-4714-3р, холеретическая терапия, урсодезоксихолевая кислота, дети*

Abstract. Influence of choleric therapy on the microRNA-4714-3p expression level in children with functional disorders of the gallbladder and Oddi's sphincter. Abaturov A.E., Babych V.L. *The high prevalence and possibility of transformation of functional disorders into organic pathology determine the relevance of the study of the cluster of functional disorders of the gallbladder and Oddi's sphincter (FD GB and OS) in children. Studies on the properties of ursodeoxycholic acid (UDCA) to alter the activity of generation of some microRNAs in various diseases of the hepatobiliary system have become important in view of the evidential impact on this process. The aim: to determine the effect of choleric therapy with UDCA drugs addition on the microRNA-4714-3p expression level in functional disorders of the gallbladder and Oddi's sphincter in children. 70 children with FD GB and OS aged 4 to 14 years were examined. Main group included 50 children. They received standard therapy with UDCA combination. The comparison group included 20 patients receiving standard therapy without UDCA. A molecular genetic study was conducted to determine the microRNA-4714-3p expression level in serum before and after treatment by real-time polymerase chain reaction with reverse transcription according to TaqMan Gene Expression Assays. The correlation was established between the main anamnestic data, causative factors of development, clinical and paraclinical parameters of the FD GB and OS and the microRNA-4714-3p expression level in blood serum of children before therapy. The positive relationship of the microRNA-4714-3p expression profile with decrease in gallbladder contractility was determined ($r=+0.36$; $p<0.05$). It has been determined that in children with FD GB and OS after the combined therapy with UDCA, the mean value of the microRNA-4714-3p expression level in serum is significantly lower than before therapy (1.93 ± 0.58 SU and 5.56 ± 1.50 SU, respectively). A positive correlation was found between the microRNA-4714-3p expression level and the alkaline phosphatase activity level in the blood of children with FD GB and OS after therapy with UDCA addition ($r=+0.33$; $p<0.05$). There was no correlation between the microRNA-4714-3p expression level and the anamnestic, clinical-paraclinical parameters in children with FD GB and OS after treatment without UDCA. The effect of UDCA on the treatment of functional disorders of the gallbladder and Oddi's sphincter in children results in a decrease in the microRNA-4714-3p expression profile and is accompanied by the emergence of a direct correlation between low level of a microRNA-4714-3p expression and reduced alkaline phosphatase activity in serum.*

Реферат. Вплив холеретичної терапії на рівень експресії мікроРНК-4714-3p у дітей з функціональними розладами жовчного міхура та сфінктера Одді. Абатуров О.Є., Бабич В.Л. *Значна розповсюдженість та можливість трансформації функціональних порушень в органічну патологію зумовлюють актуальність дослідження кластера функціональних розладів жовчного міхура та сфінктера Одді (ФР ЖМ та СФО) у дітей. Дослідження щодо властивостей урсодезоксихолевої кислоти (УДХК) змінювати активність генерації деяких мікро-РНК при різних захворюваннях гепатобілярної системи набули важливого значення з огляду на доказовість впливу на цей процес. Мета роботи: визначити вплив холеретичної терапії з додаванням препаратів УДХК на рівень експресії мікроРНК-4714-3p при ФР ЖМ та СФО в дітей. Матеріали та методи. Обстежено 70 дітей з ФР ЖМ та СФО віком від 4 до 14 років. До основної групи увійшло 50 дітей, які отримували стандартну терапію в поєднанні з УДХК. Групу порівняння склали 20 пацієнтів, які отримували стандартну терапію без УДХК. Молекулярно-генетичне дослідження проведено з визначенням рівня експресії мікроРНК-4714-3p у сироватці крові до початку й після закінчення лікування методом полімеразної ланцюгової реакції в реальному часі зі зворотньою транскрипцією згідно з протоколом TaqMan Gene Expression Assays. Результати. Встановлено взаємозв'язок між основними анамнестичними даними, зумовлюючими чинниками розвитку, клінічно-параклінічними параметрами перебігу ФР ЖМ та СФО та рівнем експресії мікроРНК-4714-3p у сироватці крові дітей до проведення терапії. Визначено позитивний взаємозв'язок профілю експресії мікроРНК-4714-3p зі зниженням швидкості жовчного міхура ($r=+0,36$; $p<0,05$). У дітей з ФР ЖМ та СФО після проведеної терапії в поєднанні з УДХК середнє значення рівня експресії мікроРНК-4714-3p у сироватці крові було вірогідно нижче, ніж до терапії ($1,93\pm 0,58$ УО та $5,56\pm 1,50$ УО відповідно). Виявлено позитивний кореляційний взаємозв'язок між рівнем експресії мікроРНК-4714-3p та рівнем активності лужної фосфатази у крові дітей з ФР ЖМ та СФО після терапії з додаванням УДХК ($r=+0,33$; $p<0,05$). Кореляційних взаємозв'язків між рівнем експресії мікроРНК-4714-3p та анамнестичними, клініко-параклінічними параметрами в дітей із ФР ЖМ та СФО після лікування без УДХК не було виявлено. Висновки. Вплив УДХК при лікуванні функціональних розладів жовчного міхура та сфінктера Одді в дітей призводить до зниження профілю експресії мікроРНК-4714-3p та супроводжується появою прямого кореляційного взаємозв'язку між зниженим рівнем експресії мікроРНК-4714-3p та зниженою активністю лужної фосфатази в сироватці крові.*

Actuality of functional disorders of the gallbladder and Oddi's sphincter (FD GB and OS) in children is due to their considerable prevalence. According to the provisions of the Order of the Ministry of Health of Ukraine dated 29.01.2013 N 59 "On approval of unified clinical protocols of medical care for children with diseases of the digestive system", the functional disorders of the

gallbladder and Oddi's sphincter make up 65-85% of all diseases of the biliary tract in children [6]. In recent years the possibility of transition of functional disorders of the biliary system into organic pathology [5] of great importance in the issue of relevance.

The results of modern scientific and practical research substantiate the use of epigenetic factors of

regulation of gene expression at the post-transcriptional level, namely, microRNA, as highly sensitive, specific diagnostic and prognostic markers for the diagnosis of diseases of the biliary system [1; 8-10; 12; 13]. In 2016, a group of scientists led by Teppei Sakamoto published the results of the study, which found that the definition of the microRNA-4714-3p expression profile is an important parameter in deciphering the mechanisms of development of primary liver biliary cirrhosis. Scientists have determined the effect of ursodeoxycholic acid (UDCA) on the microRNA expression level in primary biliary cirrhosis of the liver and indicated the effectiveness of its use [11].

Hepatoprotective, choleric, litholytic, anti-fibrotic, anti-apoptotic, cytoprotective, immunomodulatory effects of UDCA are defined in such diseases as functional disorder of the biliary system, primary biliary cirrhosis of the liver, primary sclerosing cholangitis, chronic active hepatitis, cystic fibrosis, biliary atresia, cholestasis, cholesterol stones gallbladder, biliary reflux esophagitis and reflux esophagitis [2; 3; 7; 14]. Only in recent years, scientists from different countries have drawn attention to the study of the properties of ursodeoxycholic acid to change the activity of some microRNA generation in various diseases of the hepatobiliary system [1; 11]. However, the influence of choleric therapy with the use of ursodeoxycholic acid drugs on the activity of epigenetic mechanisms, change in the microRNA expression spectrum, functional disorders of the gallbladder and Oddi's sphincter in children has not been determined yet.

Objective – to determine the effect of choleric therapy with adding of ursodeoxycholic acid drugs on the microRNA-4714-3p expression level in functional disorders of the gallbladder and Oddi's sphincter in children based on the study of the relationship between the microRNA-4714-3p expression profile and anamnestic, clinical- paraclinical parameters of functional disorders of the biliary system in children.

MATERIALS AND METHODS OF RESEARCH

In order to achieve this aim, a comprehensive examination of 70 children with FD GB and OS aged from 4 to 14 years old was conducted on the basis of the municipal institution "Dnipro city clinical hospital N 1" Dnipro city Council, Dnipro city, Ukraine. To establish the diagnosis, the provisions of the Order of the Ministry of Health of Ukraine dated 29.01.2013 N 59 "On Approval of Uniform Clinical Protocols for Medical Aid to Children With Digestive Disorders" were used [6] and Rome IV consensus on the functional

gastrointestinal disorders (2016) [4] based of the results of clinical-anamnestic, general-clinical, biochemical, instrumental research methods. Criteria for inclusion in the study: the age of children from 1 to 18 years old and with diagnosed functional disorders of the gallbladder and Oddi's sphincter. Exclusion criteria: the age of a child less than 1 year, the presence of symptoms of organic damage to the digestive system, the presence of acute (or decompensated) diseases. Scientific research was conducted with informed consent from parents or guardians of patients and practically healthy children in accordance with the principles of the Helsinki Declaration and with the permission of the local Bioethics Commission of the State Institution «Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine».

Patients with FD GB and OS were divided into two groups by simple randomization. Main group included 50 children with FD GB and OS, who received standard therapy combined with ursodeoxycholic acid, calculated as 10-15 mg/kg/day in accordance with the provisions of the Order of the Ministry of Health of Ukraine dated 29.01.2013 N 59. The comparison group was made up of 20 patients with FD GB and OS, who received standard therapy in accordance with the provisions of the Ministry of Health of Ukraine dated 29.01.2013 N 59 without ursodeoxycholic acid. The course of treatment was 4 weeks. After the completion of the course of integrated therapy in combination with or without a ursodeoxycholic acid based on the dynamics of complaints, objective data, results of biochemical, instrumental research methods, the effectiveness of treatment was evaluated. Control group included 20 practically healthy children. There were no apparent differences in the gender-age indices in the groups of the examined children.

A molecular genetic study was conducted with determining the microRNA-4714-3p expression level in serum before and after therapy in children with FD GB and OS, and one time in for practically healthy children. It was performed according to the Taq Man Gene Expression Assays Protocol in the certified laboratory of the Department of General and molecular Pathophysiology of the Institute of Physiology named after A.A. Bogomolets of NAS of Ukraine (Head - Doctor of Medical Science, Professor A.A. Krishtal). The study included the following steps: isolation of total RNA from the primary material (blood serum); reverse transcription; polymerase chain reaction (PCR); restriction analysis; polymerase-chain reaction in real time; calculation of the number of amphilic molecules and construction of the calibration curve.

Statistical analysis of the results was performed using the STATISTICA 6.1 application package (AGAR909E415822FA) using a personal computer based on the Intel Pentium 4 processor. Parametric and nonparametric statistical methods were used depending on the result of the test. Quantitative indices are given in the form of mean and standard mean error ($M \pm m$), for comparing the averages in all groups, the Student t-criterion was used. The differences between the comparable features for all types of analysis were considered statistically significant at $p < 0.05$. The clinical-laboratory and instrumental-diagnostic parameters of 70 patients with verified functional disorders of the gallbladder and Oddi's sphincter with the help of correlation analysis were analyzed. To estimate the relationship between quantitative features, a correlation analysis using the Pearson method was used, and between qualitative characteristics – the Spearman (r_s) nonparametric ranking analysis. Only significant correlations were taken into account ($p < 0,05$).

RESULTS AND DISCUSSION

The microRNA expression level in blood serum in functional disorders of the gallbladder and Oddi's sphincter before therapy

According to the results of the molecular genetic study, it was determined that in the FD GB and OS, the microRNA-4714-3p expression level in the blood serum was 5.56 ± 1.50 SU in the children of the main group and 4.66 ± 1.57 SU in patients of the comparison group and did not differ significantly in these groups ($p > 0.05$) [2]. It was found that the microRNA-4714-3p expression level in both clinical groups was low and significantly different from the values in the control group (42.77 ± 5.43) ($p < 0.05$). Correlation diagram of the relationship between the microRNA-4714-3p expression level and the anamnestic, clinical and paraclinical parameters in children with FD GB and OS before treatment presented a number of correlation interactions (Fig. 1).

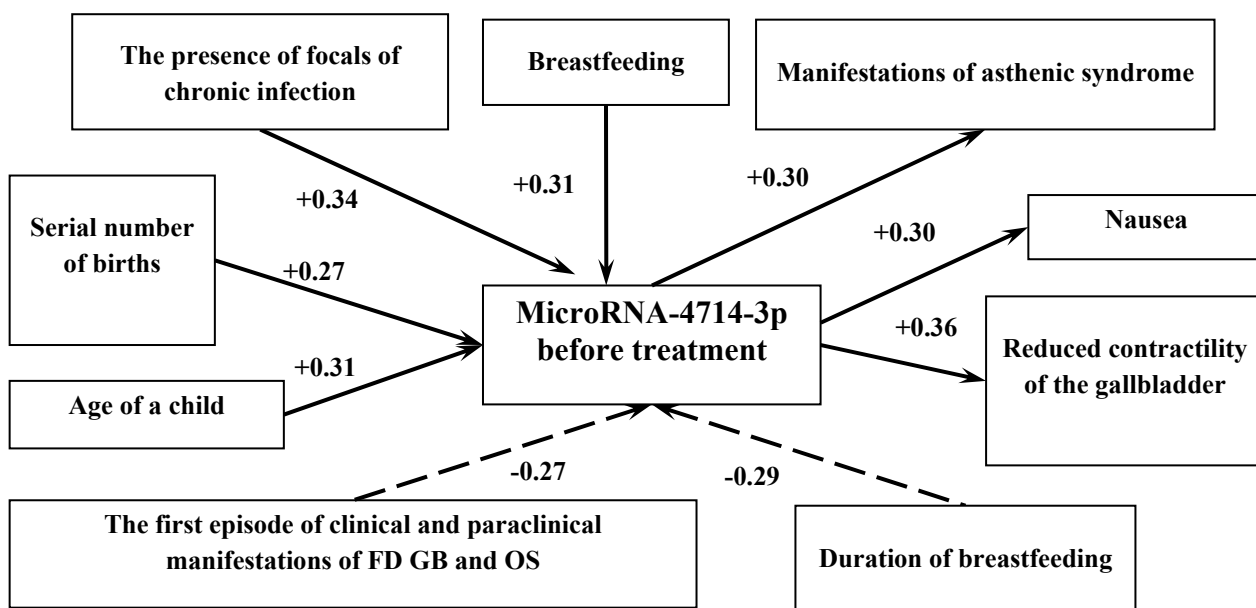


Fig. 1. Correlation diagram of the relationship between the microRNA-4714-3p expression level in serum and anamnestic, clinical-paraclinical parameters in children with FD GB and OS before therapy

The correlation was established between the main anamnestic data determining the factors of development, the clinical and paraclinical parameters of FD GB and OS and the marker of the epigenetic mechanisms of functional disorders of the biliary tract, namely, the microRNA-4714-3p expression level in the blood serum of the children before therapy.

Age and gender of a child

Significant differences in age and gender in the primary and in the comparison group were not

observed. The average age of children in the main group was 7.84 ± 0.39 , and in the comparison group – 8.90 ± 0.52 years ($p > 0.05$). In the main group boys prevailed (29 (58%) and 21 (42%) respectively), and in the comparison group, the gender distribution was equal (10 (50%) and 10 (50%) respectively) ($p > 0.05$). Correlation analysis revealed a positive correlation between the microRNA-4714-3p expression level and the age of patients with FD GB and OS ($r = +0.31$; $p < 0.05$).

The first episode of clinical and paraclinical manifestations of FD GB and OS

The study found that the first episode of clinical and paraclinical manifestations of FD GB and OS was observed in 28 (56%) children in the main group and in 12 (60%) patients in the comparison group ($p>0.05$). The average age of the manifestation of the disease in the examined of the main group and in the comparison group was 6.76 ± 0.35 and 8.00 ± 0.58 years, respectively ($p>0.05$). In the correlation diagrams, the relationships between the microRNA-4714-3p expression level and the first episode of clinical and paraclinic manifestations ($r=-0.27$; $p<0.05$) are shown in the inverse correlation relationship.

Perinatal history

The positive correlation between the microRNA-4714-3p expression level and the serial number childbirth ($r=+0.27$; $p<0.05$) was determined.

45 (90%) children of the main group and 19 (95%) of the comparison group patients ($p>0.05$) were on natural breastfeeding after birth. The duration was 10.67 ± 0.89 months and 7.63 ± 1.20 months of life, respectively ($p<0.05$). There was a positive correlation between the miRNA-4714-3p expression level and the breastfeeding ($r=+0.31$; $p<0.05$) and negative – with the duration of breastfeeding ($r=-0.29$; $p<0.05$).

Factor contributing to the onset or aggravation of the clinical course of functional disorders of the gallbladder and Oddi's sphincter in children

Chronic infection foci (7 (14%) and 4 (20%), respectively) were found to be a contributory factor to the onset or exacerbation of the disease course in patients with FD GB and OS, so correlation analysis revealed a positive relationship between the level of microRNA-4714-3p and the factor of the presence of foci of chronic infection ($r=+0.34$; $p<0.05$).

Clinical-paraclinical manifestations of functional disorders of the gallbladder and Oddi's sphincter before therapy

On admission to the hospital, all children experienced symptoms of painful abdominal, dyspeptic and asthenic syndromes of FD GB and OS. In 9 (18%) children in the main group and 4 (20%) in the comparison group abdominal pain was localized in the right hypochondrium, and in 28 (56%) and 13 (65%) patients respectively – in the epigastric region and right hypochondrium, in 13 (26%) and 3 (15%) of those surveyed – in the peritoneal region respectively. On palpation of the abdomen, pain in the right hypochondrium was determined in 42 (84%) patients of the main group and 18 (90%) children of the comparison group. Positive Kerr symptom was

found in all children. Positive Murphy symptom was found in 38 (76%) children of the main group and 16 (80%) children of the comparison group. Pancreatic pain (Dezharden, Mayo Robson, Schoffar zone) was found in 10 (20%) patients in the main group and 6 (30%) children of the comparison group. Patients with FD GB and OS before treatment had complaints of nausea (22 (44%) and 8 (40%) respectively, decreased appetite (26 (52%) and 9 (45%)), bitter belching (11 (22%) and 4 (20%)), unstable bowel voiding (23 (46%) and 5 (25%)) ($p>0.05$). A positive correlation between the microRNA-4714-3p expression level and the manifestation of dyspeptic syndrome (nausea) was found ($r=+0.30$; $p<0.05$). Asthenic syndrome in children with FD GB and OS before treatment included complaints and manifestations of reduced working capacity, fatigue, general weakness in 34 (68%) children of the main group and 14 (70%) patients of the comparison group [2]. As a result of the correlation analysis, a direct relationship between the microRNA-4714-3p activity level and the signs of asthenic syndrome ($r=+0.30$; $p<0.05$) was determined.

Indicators of biochemical hepatogram in children with FD GB and OS of the main group and the comparison group before treatment showed signs of cholestasis, namely changes in the aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase levels in normal levels of cholesterol, total and direct bilirubin in serum. As a result of the biochemical study, the statistically significant increase in the content of AsAT in the blood serum up to 34.96 ± 1.31 $\mu\text{mol/l}$ was found to in the children of the main group and up to 28.20 ± 1.31 $\mu\text{mol/l}$ in the comparison group ($p>0.05$) in relation to the corresponding value in practically healthy children (24.20 ± 0.89 $\mu\text{mol/l}$) ($p<0.05$). The ALT level in the blood serum of children in the main group was significantly different from that of the control group (18.76 ± 0.91 n/l and 14.50 ± 0.57 n/l respectively) ($p<0.05$). The content of alkaline phosphatase in serum was 507.92 ± 19.94 n/l in patients in the main group and 542.85 ± 40.95 n/l in children in the comparison group ($p>0.05$), which is statistically higher than 202.95 ± 9.07 n/l in children of the control group ($p<0.05$) [2].

According to the results of dynamic transabdominal ultrasonography in patients with FD GB and OS, decreased contractility of the gallbladder at defecation was noted. In children who subsequently received UDCA, the contractility of the gallbladder averaged $23.44\pm 1.56\%$, and in children who did not receive UDCA – $23.75\pm 2.29\%$ ($p>0.05$) [2]. The indicators of both groups of observation were significantly different from the mean contractile function

of almost healthy children – $49.55 \pm 1.11\%$ ($p < 0.05$). As a result of the correlation analysis in the examined children, a positive relationship was found between the microRNA-4714-3p expression profile and decreased gallbladder contractility ($r = +0.36$; $p < 0.05$).

MicroRNA expression level in serum in functional disorders of the gallbladder and Oddi's sphincter after therapy

According to our research, it has been determined that in children with FD GB and OS after treatment with ursodeoxycholic acid, the mean value of the microRNA-4714-3p expression level in serum is significantly lower than before therapy (1.93 ± 0.58 SU and 5.56 ± 1.50 UO respectively) ($p < 0.05$) [2].

The correlation between the microRNA-4714-3p expression level and the paraclinical parameter of the FD GB and OS in children after treatment with UDCA is shown in the diagram (Fig. 2).

It was found that in children with FD GB and OS after treatment without UDCA, the micro-RNA-4714-3p expression profile in serum was 1.14 ± 0.53 SU [2]. The indicated values significantly differed from the similar indicator in children of comparison group before therapy (4.66 ± 1.57 SU) ($p < 0.05$). However, there was no correlation between the microRNA-4714-3p expression level and anamnestic, clinical-paraclinical parameters in children with FD GB and OS after treatment without UDCA.

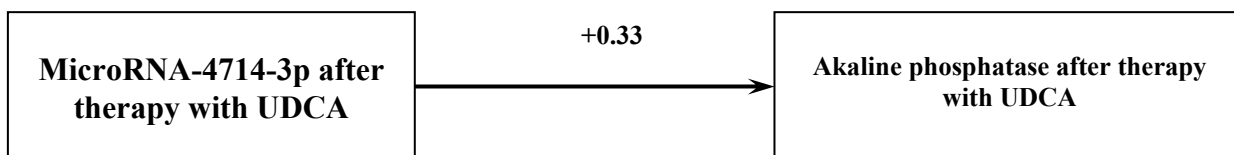


Fig. 2. Correlation diagram of the relationship between the microRNA-4714-3p expression level in serum and paraclinical parameter in children with FD GB and OS after therapy with UDCA

Clinical-paraclinical manifestations of functional disorders of the gallbladder and Oddi's sphincter after therapy

After therapy in children of the main group with FD GB and OS, complete disappearance or statistically significant decrease in the signs of painful abdominal syndrome, complete absence of dyspeptic manifestations and a possible decrease in the symptoms of astenic syndrome were determined. At the same time, in patients of the comparison group, the signs of the above-mentioned clinical syndromes of FD GB and OS persist. Complaints of pain localized in the epigastric region and the right hypochondrium after treatment were in only 2 (4%) patients of the main group, and complaints of pain in

the right hypochondrium – in 6 (30%) children of the comparison group. Complaints of nausea and appetite are observed in 3 (15%) children in the comparison group after treatment. Signs of asthenic syndrome, namely, complaints and manifestations of reduced productivity, increased fatigue, and general weakness after treatment remain in 9 (18%) patients of the main group and in 11 (55%) children of the comparison group [2].

The dynamics of biochemical hepatogram indices in children of the main group and the comparison group with FD GB and OS before and after standard therapy with and without UDCA has probable differences ($p < 0.05$) (Table).

Results of biochemical study of serum in children with functional disorders of the gallbladder and Oddi's sphincter before and after treatment (M±m)

Blood biochemical parameters	Children, who received UDCA (n=50)		Children, who did not received UDCA (n=20)		Practically healthy children (n=20)
	before treatment	after treatment	before treatment	after treatment	
Cholesterol, mmol/l	3.82±0.09	3.51±0.09	3.72±0.15	3.51±0.14	3.76±0.12
Alkaline phosphatase, n/l	507.92±19.94 *	359.53±16.59**	542.85±40.95 *	499.50±40.16	202.95±9.07
Total bilirubin, μmol/l	12.13±0.55	11.55±0.39	13.93±0.93	13.28±0.60	11.50±0.68
Direct bilirubin, μmol/l	1.43±0.11	1.35±0.11	1.54±0.19	1.71±0.38	1.32±0.14
Aspartate aminotransferase, n/l	34.96±1.31 *	26.18±0.97 **	28.20±1.31 *	29.65±1.66	24.20±0.89
Alanine aminotransferase, n/l	18.76±0.91 *	14.96±0.64	17.35±1.52	15.90±1.22	14.50±0.57

Notes: * - $p < 0.05$ – probability of differences compared with the parameter value in healthy children; ** - $p < 0.05$ – probability of differences compared with the parameter value before treatment.

After conducting complex therapy with the UDCA adding, a significant decrease in the markers of cholestasis, namely, the level of aspartate aminotransferase and alkaline phosphatase in serum ($p < 0.05$) in the examined children was found. In children, who did not receive UDCA therapy, after the course of treatment, the biochemical parameters of blood do not have a significant change ($p > 0.05$). Correlation analysis revealed a positive correlation between the microRNA-4714-3p expression level and the alkaline phosphatase activity level in the blood of children with FD GB and OS after therapy with UDCA adding ($r = +0.33$; $p < 0.05$).

According to the data of dynamic transabdominal ultrasonography after the treatment in children of the main group, there is a significant increase in the dynamic contractility in the gallbladder emptying up to $45.56 \pm 1.68\%$ ($23.44 \pm 1.56\%$ before treatment) ($p < 0.05$). In children of the comparison group, the contractile function of the gallbladder remains low and the mean value of its index is $29.69 \pm 2.99\%$ ($23.75 \pm 2.29\%$ before treatment) ($p > 0.05$).

The study determined the important role of the duration of breastfeeding, the presence of foci of chronic infection in the formation of FD GB and OS in children. The correlation between the microRNA-4714-3p expression level and the clinical symptoms of dyspeptic and asthenic syndromes in children with FD GB and OS may be due to the indirect participation of microRNA in the synthesis of proteins, the differentiation of cells and tissues. Reduce in the contractile function of the gallbladder in children with FD GB and OS correlates with the relatively low microRNA-4714-3p expression level, which is probably due to the effect of epigenetic mechanisms on the motor-evacuation function of the biliary system.

Expressed positive clinical dynamics after complex therapy with ursodeoxycholic acid adding may indicate an improvement in the rheological

properties of bile. Positive correlation between the microRNA-4714-3p expression level and the alkaline phosphatase activity level in the blood of children with FD GB and OS after therapy with the addition of UDCA can be explained by the choleric effect of UDCA on the physical and chemical properties of bile with increasing its hydrophilicity. We assume that the microRNA-4714-3p expression level before treatment in children of both groups was associated with a decrease in the contractile function of the gallbladder in children with FD GB and OS. Analysis of the dynamics of gallbladder contractility before and after treatment revealed a significant increase in the contractile function of the gallbladder in the children of the main group, which may be explained by the positive effect of UDCA on the contractility of the gallbladder.

CONCLUSIONS

1. Relatively low level of MicroRNA-4714-3p expression in serum is associated with dyspeptic (nausea), asthenic syndromes and decreased gallbladder contractility in children with functional disorders of the gallbladder and Oddi's sphincter.

2. The effect of ursodeoxycholic acid in the treatment of functional disorders of the gallbladder and Oddi's sphincter in children results in a decrease in the microRNA-4714-3p expression profile and is accompanied by a direct correlation between microRNA-4714-3p expression low level and reduced alkaline phosphatase activity level in serum.

3. The use of ursodeoxycholic acid drugs in functional disorders of the gallbladder and Oddi's sphincter in children leads to a regression of symptoms of dyspeptic and asthenovegetative syndromes, normalization of biochemical markers of cholestasis, and increased gallstone contractility.

4. Conflicts of interest: author has no conflict of interest to declare.

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