УДК 616.366-003.7-053.2]-616-092-08 Original research

# *THE LEVEL OF ZINC IN BLOOD PLASMA AND THE COURSE OF GALLSTONE DISEASE IN CHILDREN*

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***Key words:*** *children, biliary tract dysfunction, gallstone disease, clinical and laboratory course, zinc.*

*Bukovinian Medical Herald.*

*2023. V. 27, № 1 (105). P. 61-66.*

***DOI:*** *10.24061/2413-0737.27.1.105.2023.11*

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*Determining the zinc level in children's blood plasma is an urgent problem, given its possible participation in the formation of cholelithiasis.*

***Aim.*** *To investigate the level of zinc in the blood plasma and the clinical course of gallstone disease (GSD) in children.*

***Methods.*** *69 children aged 10-17 years and 25 children without biliary tract pathology were selected by the method of simple randomization. Verification of the diagnosis was carried out by applying dynamic ultrasound examination and X-ray examination of the organs of the abdominal cavity. Quantitative determination of zinc in blood plasma was carried out using mass spectrometry.*

***Results.*** *Dysfunction of the biliary tract according to the hyperkinetic type occurred in 55.1±7.1% of children and according to the hypokinetic type in 44.9±3.9%. The asymptomatic variant of housing and communal services was observed in 23.9%, painful - in 54.3% of patients, paroxysmal - in 21.7% of patients. The plasma concentration of zinc in children with gastrointestinal diseases was 1.87 times lower than in children of the comparison group and 1.37 times lower than in children with hyperkinetic gallbladder dysfunction, while there was a probable difference between these indicators in children with housing and communal services and in children with the hypotonic type of gallbladder dysfunction ($p<0.05$).*

***Conclusions.*** *1. The leading syndromes of gallstone disease in children were pain and dyspepsia. 2. Gallstone disease in children occurs against the background of gallbladder dysfunction with a predominance of the painful course, the formation of solitary bilirubin-derived concretions and minor changes in biochemical blood analysis. 3. The concentration of zinc in the blood plasma of children with gallstone disease is probably lower than in children of the comparison group and does not depend on age and gender.*

# *РІВЕНЬ ЦИНКУ В ПЛАЗМІ КРОВІ ТА ПЕРЕБІГ ЖОВЧНОКАМ'ЯНОЇ ХВОРОБИ У ДІТЕЙ*

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***Ключові слова:*** *діти, дисфункція біліарного тракту, жовчнокам'яна хвороба, клінічно-лабораторний перебіг, цинк.*

*Буковинський медичний вісник. 2023. Т. 27, № 1 (105). С. 61-66.*

*Визначення рівня цинку в плазмі крові дітей є актуальною проблемою з огляду на його можливу участь у формуванні холелітіазу.*

***Мета.*** *Дослідити рівень цинку в плазмі крові та клінічний перебіг жовчнокам'яної хвороби (ЖКХ) у дітей.*

***Матеріал і методи.*** *Методом простої рандомізації відібрано 69 дітей віком 10-17 років та 25 дітей без патології біліарного тракту. Верифікація діагнозу проводилася з використанням динамічного ультразвукового дослідження та оглядової рентгенографії органів черевної порожнини. Кількісне визначення цинку в плазмі крові здійснювали за допомогою мас-спектрометрії.*

***Результати.*** *Дисфункція біліарного тракту за гіперкінетичним типом траплялася у 55,1±7,1% дітей та за гіпокінетичним типом у 44,9±3,9%. Асимптомний варіант ЖКХ спостерігався у 23,9%, больовий - у 54,3% хворих, нападоподібний - у 21,7 % хворих. Плазмова концентрація цинку в дітей, хворих на ЖКХ, була в 1,87 раза нижчою, ніж у дітей групи порівняння та в 1,37 раза нижчою ніж у дітей із дисфункцією жовчного міхура за гіперкінетичним типом, тоді як вірогідної різниці між цими показниками у дітей, хворих на ЖКХ та у дітей із дисфункцією жовчного міхура за гіпотонічним типом не виявлено ($p<0,05$).*

***Висновки.*** *1. Провідними синдромами жовчнокам'яної хвороби в дітей - больовий та диспепсичний. 2. Жовчнокам'яна хвороба в дітей проходить на*

*тлі дисфункції жовчного міхура з переважанням больового варіанта перебігу, утворенням одиноких білірубінового походження конкрементів та незначних змін біохімічного аналізу крові. 3.Концентрація цинку в плазмі крові дітей, хворих на жовчнокам'яну хворобу, вірогідно нижча, ніж у дітей групи порівняння та не залежала від віку та статі.*

**Introduction.** The frequency of diseases of the hepatobiliary system among the pathologies of the digestive organs in children is 1-2%, while its constant growth is noted every year [1]. Diseases of the biliary tract, as a rule, attract the attention of specialists in "adult" practice [4]. The incidence of gallstone disease is 10-20% of the adult population [5, 6] and up to 1% of the children's population [7-9]. However, this problem is becoming more and more relevant in pediatrics as even in newborn children, gallstones are becoming more and more common [10-12].

The prevalence of gallstone disease among children is not exactly known, according to some data it is from 0.1 to 1% [13-15]. Gallstone disease occurs more often in school-aged children, among children up to 7 years old, boys are twice as often affected as girls, at the age of 7-9 years there are no gender differences in the frequency of the disease, at the age of 10-12 years, girls are affected twice as often as boys. Most children have bilirubin calculi before puberty, and cholesterol calculi in puberty and adolescence [16, 17, 18]. Dyscholia of hepatic genesis, cholestasis and inflammation are the main factors in the formation of cholelithiasis in children. As a result of a genetic or acquired defect, the ratio of the main components of bile, which are synthesized in the liver, is disturbed - the liver produces lithogenic bile [19, 20]. It has been proven that an elevated level of zinc plays a certain role in the formation of stones in the gallbladder, as it is known about its ability to activate crystallization processes in certain concentrations [21, 22]. Therefore, the determination of the level of zinc in children's blood plasma is an urgent problem in view of its possible participation in the formation of cholelithiasis.

**Aim**. To investigate the level of zinc in blood plasma and the clinical course of gallstone disease in children.

**Methods**. By the method of simple randomization, 69 children aged 10-17 years were selected, pre-stratified according to the presence of biliary tract dysfunction and stones in the gall bladder, of which 46 children had the disease code according to ICD-10 – K80. The comparison group consisted of 25 children of the appropriate age without biliary tract pathology.

The cumulative frequency of complaints for each child was evaluated separately with the following gradation: periodic complaints were evaluated with a coefficient of 0.3, frequent complaints with a coefficient of 0.5, absence of complaints with a coefficient of 0.0 (maximum 2.5 points). The expression of clinical symptoms was evaluated according to the point system (from 1 to 3 points). The objective examination was carried out according to generally accepted clinical methods (palpation and percussion of the anterior abdominal wall, symptoms of G. Kerr, J. Murphy, N. Ortner were determined). Verification of the diagnosis was carried out in accordance with the unified clinical protocol [22] with the use of dynamic ultrasound examination and X-ray examination of the abdominal organs to determine the X-ray contrast of the calculi.

Blood sampling was carried out in the procedure room from the elbow vein in the morning on an empty stomach in a volume of at least 5 ml in a regular glass tube without the use of a coagulation activator. After centrifugation, the plasma was transferred to test tubes and stored at a temperature of -70 ºC until analysis. Biochemical analysis of blood was carried out according to generally accepted methods. Quantitative determination of zinc in blood plasma was carried out using inductively coupled plasma mass spectrometry (MS-ICP) on an Optima 2000 DV spectrometer (PerkinElmer, USA). The concentration was estimated in μg/l.

Data from clinical observations were statistically processed on a computer using Microsoft Excel 2010, Statistica 6.1 licensed programs. To evaluate the research results, the following indicators were studied: sufficient sample size (n), arithmetic mean (M), mean square deviation (sx), coefficient of variation (Cv), error of the mean square deviation (m), confidence limits and reliable difference of the difference of results. The averaged data are given as M±m, where M is the arithmetic mean value, m is the error of the arithmetic mean. The normality of the distribution of indicators was assessed using the Shapiro-Wilk W-test. To reveal the statistical difference between indicators in normally distributed groups, the Student's t-criterion of reliability was used, the degree of significance - p.

**Results and discussion**. The average coefficient of the frequency of complaints for each child was 0.8. In 18.9% of children, the total coefficient did not exceed 0.6, that is, the presence of complaints was sporadic, in the remaining 71.0% of the interviewed children, the frequency coefficient of complaints exceeded 1.1. More often, children complained of abdominal pain, which occurred in 78.3% of cases. Complaints about frequent abdominal pain were expressed by 4.1% of the interviewed children, 74.2% noted periodic abdominal pain. The second most frequent complaint was burping, which was often observed in 13.2% of children and occasionally in 52.7%. In third place were complaints of nausea - 52.7%. At the same time, nausea was often observed in 4.3% of children, periodically in 48.8% of children. Vomiting was observed in almost a third of children (28.9%), frequent episodes of vomiting were observed in 5.7% of children, periodic episodes in 23.2% of children. Heartburn was recorded in 20.3% of children (Fig. 1)

During objective examination in children, the liver protruded from under the edge of the right costal arch by 1.5-2.0 cm, its surface was smooth. The consistency was soft-elastic, the edge -sharp. All children had a positive.

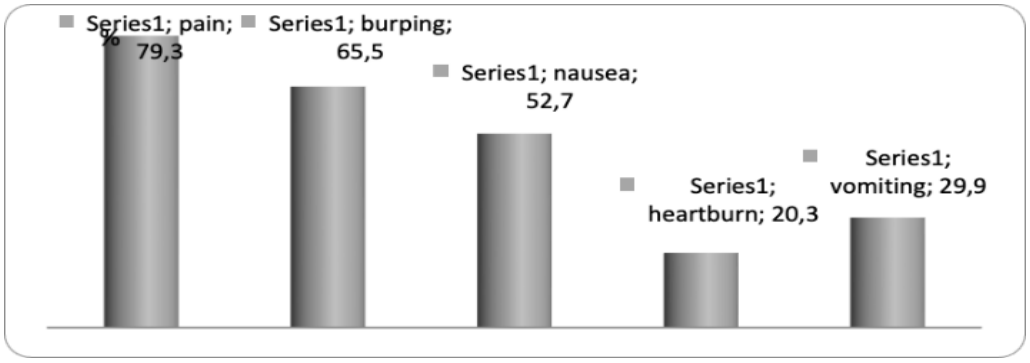


*Fig. 1. Frequency of clinical symptoms in children with functional disorders of the biliary tract*

Ortner symptom. Among the examined children, dysfunction of the biliary tract according to the hyperkinetic type occurred in 55.1±7.1% of children (n=38) and according to the hypokinetic type in 44.9±3.9% (n=31). The distribution of children with various types of biliary tract dysfunction by age is presented in Table 1.

In children aged 10-14 years, the hypokinetic variant of gallbladder dysfunction occurred more often (77.4±5.6%), while among children aged 14-17 years – hyperkinetic variant (73.7±6.3%). Girls predominate among the examined children - 56.5±7.9%. Out of 69 examined children, 46 (66.6%) were confirmed to have gallstone disease (gallstone disease). Clinical and laboratory characteristics of GSD in children are presented in Table 2. According to the stage of GSD, the children were distributed as follows: II stage - 80.4% (n=37), III stage – 19.6% (n=9). In the clinical picture of the disease, three clinical variants of the course of the disease are distinguished: the asymptomatic variant of GSD was observed in 23.9%, the painful variant of GSD – in 54.3% of patients, the paroxysmal variant of GSD with biliary colic – in 21.7% of patients. The second stage of gastrointestinal tract with single concretions, which were of pigment origin and most often localized in the gallbladder, was recorded more often. More than half of the examined children were characterized by s-shaped deformation of the gallbladder. In the biochemical blood analysis, a third of the children had an increased level of total bilirubin due to both direct and indirect factors, and some children had an increase in alkaline phosphatase and a violation of the lipid profile.

The average level of zinc in blood plasma in children with biliary tract dysfunction was 2.55 ± 0.62 mg/l, in children of the comparison group — 3.98 ± 0.69 ($p< 0.05$). We did not establish gender and age differences in zinc levels in blood plasma (Fig. 2).

*Table 1*

**Distribution of children with various types of biliary tract dysfunction by age**

| Age (years) | Hyperkinetic dysfunction, n=38 | | Dysfunction by hypokinetic type, n=31 | |
|---|---|---|---|---|
| | n | % | n | % |
| 10-12 | 10 | 26,3 | 13 | 41,9 |
| 13-14 | 13 | 34,2 | 11 | 35,4 |
| 15-17 | 15 | 39,5 | 7 | 22,5 |
| Total | 38 | 100 | 31 | 100 |

*Table 2*

**Clinical and laboratory characteristics of GSD in children**

| Indicators | Abs. | % |
|---|---|---|
| Variant of the course of the disease | | |
| asymptomatic | 11 | 23,9 |
| painful | 25 | 54,3 |
| offensive | 7 | 15,2 |
| dyspeptic | 3 | 6,5 |
| Stages | | |
| I | 9 | 19,6 |
| II | 24 | 52,1 |
| III | 13 | 28,3 |
| The number of calculi | | |
| single | 39 | 84,8 |
| multiple | 7 | 15,2 |
| Origin | | |
| cholesterol | 19 | 41,3 |
| pigmented | 20 | 44,4 |
| mixed | 7 | 15,2 |
| Localization | | |
| in the gall bladder | 30 | 65,2 |
| in the common bile duct | 15 | 32,6 |
| in the hepatic ducts | 1 | 2,2 |
| Deformation of the gallbladder | | |
| body | 8 | 17,4 |
| neck | 6 | 13,0 |
| s-like | 28 | 60,9 |
| contour | 4 | 8,7 |
| Biochemical indicators of blood | | |
| Lipidogram (mg/100ml) | | |
| Indicator | M±m | |
| total lipids | 659,3±17,3 | |
| phospholipids | 159,9±4,7 | |
| free cholesterol | 49,9±2,2 | |
| non-esterified fatty acids | 58,8±6,1 | |
| triglycerides | 175,2±9,7 | |
| cholesterol esters | 101,3±4,5 | |
| Bilirubin, mmol/l | | |
| total bilirubin | 24,8±6,1 | |
| direct fraction | 17,9±3,4 | |
| indirect fraction | 7,8±1,1 | |
| Enzymes, U/l | | |
| Alanine aminotransferase | 29,5±1,0 | |
| Aspartate transaminase | 27,9±1,1 | |
| Alkaline phosphatase | 90,9±5,7 | |

Zinc deficiency in the blood plasma of children with biliary tract dysfunction was found in 53 cases (76.8%), while in the comparison group, a decrease in zinc level was observed in only 2 children (8%). The lowest levels of zinc in the blood plasma were observed in children suffering from GSD (Table 3).

Thus, the plasma concentration of zinc in children with gastrointestinal diseases was 1.87 times lower than in children of the comparison group and 1.37 times lower than in children with hyperkinetic gallbladder dysfunction, while the probable difference between these indicators in children, there were no patients with GSD and children with hypotonic type of gallbladder dysfunction ($p<0.05$).

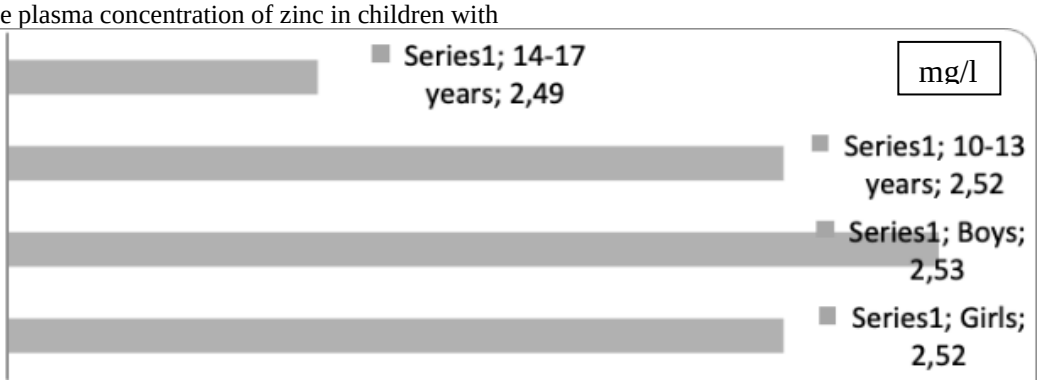


*Fig. 2. Concentration of zinc in blood plasma of examined children depending on age and gender*

*Table 3*

**Concentration of zinc in blood plasma of children with pathology of the biliary tract**

| Indicator | Children with GSD, n=46 | Children with GBD (hyperkinetic type), n=38 | Children with GBD (hypokinetic type), n=31 | CG, n=25 |
|---|---|---|---|---|
| Zinc, mg/l | 2,13±0,44* | 2,92±0,37 | 2,32±0,53* | 3,98±0,69 |

*Notes: GSD - gallstone disease, GBD - gallbladder dysfunction, CG- comparison group,*

** - the difference in indicators is probable compared to the comparison group ($p<0.05$).*

Diseases of the biliary tract are one of the most common diseases of the digestive system [23]. Disorders of the motor-evacuation function of the gallbladder are diagnosed in 70–90% of children with diseases of the digestive organs [24, 25]. These violations lead to the development of organic pathology in the following periods of life, in particular, GSD [26]. Our studies have shown that the leading syndromes of the gastrointestinal tract were pain and dyspepsia. The second stage of gastrointestinal tract with single calculi, which were of pigment origin and most often localized in the gallbladder, was recorded more often. More than half of the examined children were characterized by s-shaped deformation of the gallbladder, which is consistent with the results of other studies [16, 18, 27].

When researching the zinc content in the blood plasma, its deficiency was proven, which can be interpreted as a certain disturbance in metabolic processes or a lack of this element in the child's body due to irrational nutrition [28, 29]. Since trace elements most often perform the functions of active centers or cofactors of enzymes in the body, without correcting their metabolic disorders, it is impossible to achieve the desired results in the prevention and treatment of most pathological conditions. A large number of studies are devoted to the study of one of the essential metals - zinc [30-32]. Zinc reserves in the human body are small. It is known that an adult contains only 1.5-2 g of zinc. Zinc is a cofactor of a large group of enzymes involved in protein and other types of metabolism, so it is necessary for the normal course of many biochemical processes [33]. Zinc is involved in the processes of cell division and differentiation, the formation of T-cell immunity, the functioning of dozens of enzymes, pancreatic insulin, the antioxidant enzyme superoxide dismutase, and the sex hormone dihydrocorticosterone. Zinc plays the most important role in the processes of skin regeneration, hair and nail growth, and sebaceous gland secretion [34]. Therefore, a reduced level of zinc in the body can lead to various consequences, in particular, to impaired coordination of the motility of bile secretion. Bile formation is closely dependent on the nature of the food consumed. The amount of secreted bile, the duration of its excretion depends on the composition of the food consumed [35]. Insufficient supply of micronutrients with food can lead to a deficiency of vital biologically active substances in the body, which sooner or later leads to the development of many common diseases [36], including disorders and diseases of the gastrointestinal tract and liver [37]. Due to the properties of zinc in certain concentrations to activate crystallization processes, zinc can be involved in the process of stone formation in the gall bladder [38]. Therefore, the detection of these disorders in the early stages of the pathogenetic development of GSD is important for the purpose of including zinc-containing foods or zinc-containing preparations in the diet for the correction of zinc concentration.

**Prospects for further research**. It is considered appropriate to further study the content of zinc in the diet

of children with gallstone disease, to discuss the need to include zinc-containing drugs for the treatment of cholelithiasis.

**Conclusions**. 1. The leading syndromes of gallstone disease in children were pain and dyspepsia. 2. Gallstone disease in children occurs against the background of gallbladder dysfunction with a predominance of the painful course, the formation of solitary bilirubin-derived concretions and minor changes in biochemical blood analysis. 3. The concentration of zinc in the blood plasma of children with gallstone disease is probably lower than in children of the comparison group and did not depend on age and gender.

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***Надійшла до редакції 05.02.23***

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