NATURAL COURSE OF CHRONIC VIRAL HEPATITIS B AND C IN CHILDREN

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ЕСТЕСТВЕННОЕ ТЕЧЕНИЕ ХРОНИЧЕСКИХ ВИРУСНЫХ ГЕПАТИТОВ В И С У ДЕТЕЙ

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Annotation. Chronic viral hepatitis is a pressing problem in modern healthcare, due to the almost universal spread of this infection and the high risk of developing unfavorable outcomes. The most difficult group is represented by patients with mixed hepatitis, which is associated with more rapid progression of the disease and the development of liver cirrhosis. The article presents data from long-term observation of children with chronic hepatitis B+C (CHB+C), demonstrates the features of the clinical course, the nature of biochemical, immunological, morphological changes in the natural course of the disease.

Key words: viral hepatitis, course in children, infection, laboratory research methods, instrumental research methods.

Аннотация. Хронические вирусные гепатиты являются актуальной проблемой современного здравоохранения, что обусловлено практически повсеместным распространением данной инфекции, высоким риском формирования неблагоприятных исходов. Наиболее сложную группу представляют пациенты с микст-гепатитами, что сопряжено с более быстрым прогрессированием заболевания и формированием цирроза печени. В статье представлены данные длительного наблюдения за детьми с хроническим гепатитом В+С (ХГ В+С), продемонстрированы особенности клинического течения, характер биохимических, иммунологических, морфологических изменений при естественном течении заболевания.

Ключевые слова: вирусный гепатит, течение у детей, инфицирование, лабораторные методы исследования, инструментальные методы исследования.

Introduction. Currently, there is an increase in the number of children suffering from chronic viral hepatitis (CVH). Approximately one third of the world's population has markers of previous and about 350 million people have markers of current chronic HBV infection. About 1 million people die annually worldwide from adverse outcomes of chronic hepatitis B (liver cirrhosis and hepatocellular carcinoma). The final stages of progressive CHB are the cause of 5-10% of liver transplants performed annually [2, 15]. Currently, there are more than 180 million carriers of HBV [1, 14]. It is believed that about 5-15 million people worldwide suffer from mixed hepatitis B+C, which is characterized by a more severe clinical picture compared to monohepatitis B and C, a more rapid rate of progression, and ambiguity in approaches to therapy [2, 13].

To assess the natural course of mixed hepatitis, two conditions are important: precise determination of the date of primary infection and adequate diagnostic tools. According to literature data [2, 10], the frequency of detection of virus C in patients with chronic hepatitis B is 20%, and virus B in patients with chronic hepatitis C is 10%. Meanwhile, based on anamnestic data, it is difficult to clearly establish which of these viruses is the primary infection and which of them has a dominant role in the pathogenesis of chronic hepatitis and liver cirrhosis [3, 18].

The aim of the study: to study the natural course of chronic hepatitis associated with infection with NVU and NSU.

Material and methods of the study. The study included 38 children with chronic hepatitis B+C, 26 boys (68.4%) and 12 girls (31.6%). The observation period ranged from 1 to 18 years from the time of suspected infection (on average, 8.9 ± 0.7 years). The examination included an assessment of general clinical and biochemical blood parameters, enzyme immunoassay to determine HB3Ag, HBeAg, anti-HBe, anti-HBcor (total), anti-HCU, and polymerase chain reaction to detect HBV DNA and HCU RNA. Instrumental examination methods included ultrasound examination of the

abdominal organs, esophagogastroduodenoscopy. 11 patients underwent liver puncture biopsy with subsequent determination of the histological activity index (HAI) according to Knodell and the stage of the disease according to Desmet.

Results of the study and their discussion. Of the 38 examined children, parenteral anamnesis was aggravated in 37 patients. Clinical manifestations of acute viral hepatitis were registered in two patients (5.3%). After careful analysis of the anamnestic data, it could be assumed that the infection occurred at the age of 4.2 ± 0.5 years (from 0 to 13 years). The diagnosis was established during examination for intercurrent disease in the overwhelming majority of children (35 people), in two children - during routine examination after acute viral hepatitis, and in one child - during a medical examination. The average age of diagnosis was 6.6 ± 0.7 years (aged 1-14 years).

The clinical picture of NVU+NSU in children is characterized by few symptoms. Asthenovegetative syndrome, manifested by complaints of weakness, fatigue, was presented by 17 (44.7%) patients, arthralgia was noted in one child, skin itching - in 2 children.

Complaints of periodic abdominal pain were reported by 25 (65.8%) children, which was a manifestation of both chronic hepatitis and biliary dyskinesia in 28 (73.4%), chronic gastroduodenitis in 18 (47.4%) children, gastric ulcer in one child, and cholelithiasis in 2 patients. In the structure of concomitant diseases, the following diagnoses were confirmed in most children: chronic tonsillitis - in 13 (34.2%) children, atopic dermatitis - in 5, bronchial asthma - in 2, glomerulonephritis - in 4, chronic pneumonia - in 2 children. In the anamnesis, 16 children underwent treatment for various oncological diseases, 2 for aplastic anemia. Subicteric skin and sclera was determined in 5, telangiectasia - in 7, palmar erythema - in 4 children. Hemorrhagic syndrome, manifested by the presence of ecchymosis, was detected in 8 patients.

Liver enlargement was observed in 26 (68.4%) and spleen enlargement in 6 (15.8%) children. Given the small number of patients in the group with CHB+C, we assessed the dynamics of clinical and laboratory parameters depending on the duration of the disease during the first 5 years (n = 24), 6-10 years (n = 22) and 11-15 years (n = 15) from the time of suspected infection. With increasing duration of the disease in the examined group of children, a tendency towards a decrease in liver size was noted. During the first five years, the liver was palpated 1-5 cm below the level of the right rib (on average 1.9 ± 0.9 cm) in 69.6% of children, during the next five years - in 50%, and with a disease duration of more than 10 years - in 28.6% of patients with CHB+C. An enlarged spleen was observed in 6 children, in 5 of whom - against the background of the formation of liver cirrhosis.

A complete blood count did not reveal any significant changes at the stage of chronic hepatitis. Anemia, leukopenia and thrombocytopenia were registered in 2

children with aplastic anemia. With the development of liver cirrhosis, increasing signs of portal hypertension, and an enlarged spleen, signs of secondary hypersplenism were noted: leukopenia and thrombocytopenia (leukocytes - (2.9 ± 0.3) x 109/l, platelets - (91.3 ± 35.8) x 109/l).

The average level of both total and direct bilirubin corresponded to normal values throughout the observation period (total bilirubin 16.7 ± 1.72, direct - 2 ± 0.3 μmol/l). Cholestasis syndrome, diagnosed on the basis of increased GGT (108.1 ± 18.2 U/l), was detected in 6 (15.8%) patients with CHB+C.

The main biochemical syndrome of chronic hepatitis is cytolytic syndrome (increased levels of transaminases - ALT, AST - in the blood serum), caused by the activation of lipid peroxidation processes in hepatocytes and, as a consequence, increased permeability of cell membranes. Depending on the severity of the cytolysis syndrome, the level of enzymes can fluctuate from normal values to exceeding the norm by 10 times [1, 4, 9].

The average transaminase level did not exceed the normal value by more than 3-4 times during the entire observation period. At the onset of the disease in children with chronic hepatitis B + C, the overwhelming majority of children (36-95.8%) had elevated transaminase levels. This is consistent with the literature data. Thus, relative to chronic hepatitis C, in chronic mixed infection HBV + HCV, a minimal degree of activity is less often observed (18% versus 33%) and more often - moderate (44% versus 27%), which generally characterizes the course of chronic mixed hepatitis B + C as more severe.

As a rule, as the duration of the disease increases, a gradual increase in the number of patients with normal AST, ALT values is observed, especially in HBV or HCV monoinfection. This trend also persists in chronic hepatitis B + C. The severity of cytolysis syndrome decreased in all children with an increase in the duration of the disease.

A study of the spectrum of autoantibodies (AMA, SMA, ANA, anti-LKMl) was conducted in 18 children with CHB+C. The presence of antinuclear antibodies was detected in one child in a titer of 1/20, and antimitochondrial antibodies in two children in a titer of 1/20.

Taking into account the burdened parenteral anamnesis in the overwhelming majority of children, as well as the absence of clinical manifestations of acute viral hepatitis, irregularity of the study of hepatitis markers, it was not possible to establish the sequence of infection (coinfection of viruses, superinfection). Initially, HBsAg, HBeAg, anti-HBeog IgG, anti-HSU IgG, HV DNA, HSU RNA were detected in the blood serum of all children admitted to our observation. HSU infection in the examined group of children was associated with genotype 3a in 65%, and with genotype 1b in 35%.

The widespread use of modern methods of virological analysis, in particular polymerase chain reaction (PCR), has made it possible to clarify the predominant role of one or another virus in the development of chronic hepatitis of mixed viral etiology [2, 17]. There is a point of view on the competing relationships of NVU and NSU, in which both viruses are detected in the liver, but nucleic acids of only one of the viruses circulate in the serum. The mutual reducing effect of viruses is evidenced by the detection of a lower concentration of HBV-DNA and HBV-RNA in a combined infection than in a monoinfection [3, 19, 20]. Often, when infected with several viruses, either one or both viruses are suppressed, resulting in recovery. This phenomenon is called "virus interference" [1, 5, 6].

Dynamic observation registered seroconversion in the HBeAg/anti-HBe system in 17 (44.7%) children with CHB+C on average after 5.8 ± 1.1 years from the time of presumed infection, which was accompanied by a decrease in cytolysis syndrome (from 148.2 ± 31.8 to 61.5 ± 13.9 U/L, $p < 0.05$); a decrease in HBV DNA to an undetectable level was detected in 12 (31.6%) children after 5.3 ± 0.9 years. HBsAg elimination occurred in 12 (31.6%) patients after 6.3 ± 1.1 years.

A decrease in RNA NSU to an undetectable level in the blood was detected in 11 (28.9%) children after 7.5 ± 0.9 years, which was accompanied by a decrease in the level of transaminases from 103.4 ± 14.1 to 71.2 ± 19.8 U/L.

Determining the course of mixed hepatitis is one of the key points, given that the strategy and tactics of therapy for HBV+HCV infection have not been fully developed [2, 7]. Clarification of the mechanisms of viral interference allows not only to clarify the features of their replication, but also to develop new approaches for antiviral therapy [3, 8].

During the ultrasound examination of the abdominal cavity, a moderate increase in the left and right lobes of the liver was noted, the parenchyma of which was heterogeneous, hyperechoic. In the porta hepatis, lymph nodes were detected in 18 (47.4%) children: round formations of homogeneous structure No. 2-3, 9-15 mm in size. Signs of portal hypertension were detected in 5 children with cirrhosis of the liver as a result of CHB + C: expansion of the diameter of the trunks of the portal (up to 12 mm) and splenic veins (up to 11 mm), an increase in the size of the spleen (up to 150.1 ± 10.6 mm in length, 67.8 ± 4.9 mm in diameter), its heterogeneity, hyperechogenicity, compaction of the intraorgan branches of the splenic vein. The height of the left lobe of the liver in children with cirrhosis was 90.5 ± 18.5 mm, the right lobe - 109.1 ± 9.2 mm. Its parenchyma was also hyperechoic, heterogeneous, "stringiness" of the liver pattern was determined, in 3 children, regeneration nodes in the liver parenchyma of 7 to 18 mm in size were visualized. Esophageal varices of 1-11 degrees were detected in all children with liver cirrhosis (n = 5).

It is believed that morphological changes in the liver in children with CHB+C do not differ qualitatively from those in patients with CHB and CHC [2, 16]. In our study, histological examination of liver tissue, conducted on average 7.2 ± 4.1 years after the time of suspected infection and obtained by puncture biopsy, was performed in 11 children with CHB+C. The average histological activity index was 5.0 ± 0.3 points according to Knodell. At the same time, the minimum degree of histological activity was detected in 5 children, low - in 5, moderate - in one child.

Formation of fibrosis in patients with chronic hepatitis is the result of imbalance between the processes of synthesis and decay of the extracellular matrix with prevalence of processes of formation of extracellular matrix components. When assessing the stage of fibrosis and disturbances of liver architecture (according to Desmet), expansion of portal tracts (which corresponds to a mild degree of changes) was determined in three children, presence of porto-portal septa (moderate degree) in three patients, severe degree of fibrosis associated with bridging changes in four patients, presence of liver cirrhosis in one child, which indicates more pronounced signs of fibrosis in comparison with monohepatitis B and C (hepatitis stage 2.3 ± 0.3). The obtained data of morphological study are consistent with literature data [1, 12, 16].

Conclusions. Thus, in many patients it is difficult to determine the date of primary infection with HCV, and without this starting point, the characterization of the natural course cannot be accurate. Nevertheless, even a short experience of observing the natural course of CHC allowed us to characterize the clinical forms of the disease, as well as to determine the factors that can influence its course. The first detection of markers of hepatitis B and C in the children we observed was associated with an examination for an intercurrent disease, which confirms the latency of the course of chronic hepatitis B + C in children, the leading clinical symptoms of which at the onset of the disease are slight hepatomegaly and cytolytic syndrome.

In 17 (44.7%) children, the disease continues with moderate and high viral replicative activity for 9 years from the moment of infection, and in 18 (47.4%) it acquires features of monoinfection (B or C). The development of liver cirrhosis as a result of chronic hepatitis B+C was confirmed by us in 5 (13.2%) patients, on average, 8 years after the moment of suspected infection.

Due to the lack of a clear clinical picture of acute viral hepatitis, in order to identify viruses earlier for timely administration of antiviral therapy, all children with a burdened parenteral history need to undergo routine testing of the entire spectrum of markers of viral hepatitis B and C.

LITERATURE

1. Bellecave P. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference / P. Bellecave, J. Gouttenoire, M. Gajer et al. // J. Hepatology. — 2009. — Vol. 50. — P. 46-55.

2. Ющук Н. Д. Протокол диагностики и лечения больных вирусными гепатитами В и С / Н. Д. Ющук, Е. А. Климова, О. О. Знойко и др. // Рос. журн. гастроэнтерол., гепатол. и колопроктол. 2010. — Т. 20, № 6. — С. 4-60.
3. Айдагулова С. В. Хронический микст-гепатит С+В: клинические варианты / С. В. Айдагулова, Д. Л. Непомнящих, О.А Постникова и др. // Фундам. исследов. — 2011. — № 10, Ч. 3. — С. 457-461.
4. Ширинов Х. И., Ибрагимова Н. С., Ибрагимов Б. Ф. НЕБЛАГОПРИЯТНЫЕ ИСХОДЫ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ У МОЛОДЫХ ЖЕНЩИН //Journal of new century innovations. – 2023. – Т. 26. – №. 3. – С. 185-189.
5. Kudratova Z. E.Isomadinova L. K.Sirojeddinova S. F. Tursunova M. E.Current modern etiology of anemia. novateur publications international journal of innovations in engineering research and technology. № 10. 2023, P. 1-4.
6. Isomadinova L.K. Qudratova Z.E. Shamsiddinova D.K.Samarqand viloyatida urotiliaz kasalligi klinik-kechishining o'ziga xos xususiyatlari. Central asian journal of education and innovation №10. 2023 , P. 51-53
7. Sabirovna I. N., Fotima I. PROBLEMS OF DIAGNOSIS OF COMMUNITY ACQUISITED PNEUMONIA IN YOUNG CHILDREN //TADQIQOTLAR. UZ. – 2024. – Т. 31. – №. 2. – С. 188-192.
8. Бердиярова Ш.Ш., Юсупова Н.А. Особенности иммунометаболических нарушений иммунологической реактивности при гематогенных остеомиелитах, Вестник науки и образования, 29-32
9. Dushanova G. A., Nabiyeva F. S., Rahimova G. O. FEATURES OF THE DISTRIBUTION OF HLA-ANTIGENS AMONG PEOPLE OF THE UZBEK NATIONALITY IN THE SAMARKAND REGION //Open Access Repository. – 2023. – Т. 10. – №. 10. – С. 14-25.
10. Berdiyarova Sh.Sh., Ahadova M.M., Ochilov S.A. COMPLICATIONS OF TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS, LITERATURE REVIEW, Galaxy International Interdisciplinary Research Journal 293-298
11. Бердиярова Ш.Ш., Юсупова Н.А., Ширинов Х.И. Клинико-лабораторная диагностика внебольничных пневмоний у детей, Вестник науки и образования, 80-83
12. Kudratova Zebo Erkinovna, Karimova Linara Alixanovna Age-related features of the respiratory system // ReFocus. 2023. №1. URL: https://cyberleninka.ru/article/n/age-related-features-of-the-respiratory-system.
13. Sabirovna I. N. et al. Dysfunctions of the Immune System and Their Role in the Development of Diseases //The Peerian Journal. – 2023. – Т. 23. – С. 49-52.

14. Sabirovna I. N., Muhammadali B. LABORATORY INDICATORS OF NEPHROPATHY IN TYPE II DIABETES MELLITUS //Web of Medicine: Journal of Medicine, Practice and Nursing. – 2024. – Т. 2. – №. 5. – С. 93-95.
15. Ибрагимова Н. и др. РАССТРОЙСТВА ИММУННОЙ СИСТЕМЫ. ПАТОГЕНЕТИЧЕСКИЕ ОСНОВЫ //Центральноазиатский журнал академических исследований. – 2024. – Т. 2. – №. 1. – С. 4-8.
16. Isomadinova L.K, Qudratova Z.E., Babaxanova F.Sh.clinico-laboratory features of the course of covid-19 with hepatitis b journal of new century innovations №-3. 2023 P. 60-65.
17. Nabiyeva F. S., Ibragimova N. S., Diamatova D. N. 2-TIP QANDLI DIABET KECHISHINING O'ZIGA XOS XUSUSIYATLARI //TADQIQOTLAR. UZ. – 2024. – Т. 31. – №. 1. – С. 28-32.
18. Sadriddinovna N. F., Ugli A. S. S., Kizi O. B. K. BIOLOGICAL PROPERTIES OF THE YEAST SACCHAROMYCES CEREVISIAE //Research Focus. – 2022. – Т. 1. – №. 4. – С. 18-22.
19. Давлатов С. С., Сайдуллаев З. Я., Даминов Ф. А. Миниинвазивные вмешательства при механической желтухе опухолевого генеза периампулярной зоны //Сборник Научно-практической конференций молодых ученных СамМИ. – 2010. – Т. 2. – С. 79-80.
20. Nabiyeva F. S. et al. CREATION OF OPTIMUM CONDITIONS FOR PROPAGATION OF SACCHAROMYCES CEREVISIAE YEAST //Journal of new century innovations. – 2023. – Т. 23. – №. 1. – С. 85-91.