Administration of Proteflazid in combined therapy of children with chronic hepatitis C

T.A. Kruchko, Mohammed M.A. Abdalaal

Poltava Ukrainian State Medical and Dental Academy

Progress of hepatitis C virus at children is characterized by prevailing of subjects in reactivation phase (58.3%). The main clinical manifestations of CHC at examined children were represented by complaints of astheno-vegetal (70.8%), dyspeptic (50.0%) and bilious syndromes. Studies of central and peripheral hemodynamics showed changes of portal vein diameter, increase of pulsation index and resistance index in both phases of infectious process. The study results of interferon profile were characterized by increase of antiviral interferon-a (INF-α) by 5 times in reactivity phase. Administration of medicinal complex with inclusion of antiviral drug Proteflazid and membrane stabilizer Thiotriazolin in therapy of children with HCV contributed to decrease of virus replication intensity, increase of INF-α in latent phase and to normalizing of hemodynamic readings.

Key words: *children, hepatitis C virus, interferons b and g, hemodynamics, Proteflazid.*

Chronic viral hepatitis is reviewed by WHO as serious problem of healthcare in society due to wide spreading, progression of infection and adverse results. According to specialist assessment, from 200 million to 1 billion of people are infected with hepatitis C virus (HCV), of which not less than 350 mln have signs of chronic hepatic injury [1]. Because of specialties of progression, increasing growth of spreading and absence of effective preventive treatment, exactly hepatitis C (HC) attracts more and more attention of pediatricians, therapists and infectious disease specialists. In etiological structure of all viral hepatitis, registered in the world, hepatitis C takes around 50% [2]. Since 2003, incidents of hepatitis C virus (HCV) are registered in Ukraine, but imperfection of laboratory abilities in the regions extremely limits epidemiologic studies and timeliness of diagnosing becomes difficult.

Nowadays there is no doubt, that natural progression of HCV at most part of children is easier, but longer in comparison with infection acquired in mature age. At the same time, the question of possibility of self-healing of the subjects with CHC (chronic hepatitis C) is still discussable [3, 4]. Thus, data of various authors confirm deep and varied immune and hemodynamic violations as a result of HCV-infection. These violations play leading pathogenic role in the course of chronic inflammatory process formation [5, 6].

The aim of this work was an investigation of clinical-and-dynamic violations at children with CHC, depending on disease phase and their complex correction, with the use of Proteflazid and membrane stabilizer Thiotriazolin.

MATERIALS AND METHODS

Twenty four children, 6-15 years old, having chronic hepatitis C, were under our care at in-patient department of Poltava regional children clinical hospital. Healthy children (n=30) of the same gender and age composed the control group.

Chronic hepatitis C (CHC) diagnosis was made on the base of clinical laboratory, serologic and molecular-biological data. Serologic and molecular biological studies included determination of anti-HCV and HCV RNA. For determination of HCV RNA, the method of polymerase chain reaction (PCR) was used with test-set "Polygep-C" (Moscow). For determination of anti-HCV, the test systems of 3rd generation were used, which are based on immune fermentative analysis (IFA), manufactured by "Vector-Best" (Novosibirsk).

Hepatic fibrosis degree at the subjects under care was assessed by US-investigation. In this assessment, we used US-criteria developed by A.G. Pisarev and V.F. Uchaikin at infectious disease department of Russian state medical university (Moscow). For characterization of intrahepatic blood flow, we used Doppler velocimetry at "ALOKA" SSD-500 device by curved transducer with 3.5-5 MHz frequency. We determined portal vein diameter (V_{turn}) ad maximum speed of blood flow in portal vein (V_{max}); we calculated coefficient of arterial hemodynamics: index of resistivity ($IR=V_{max}-V_{min}/V_{max}$) and pulsation index ($PI=V_{max}/V^{min}$).

Interferon concentration in blood serum was determined with a help of commercial sets for ELISA test ("Vector-Best", Novosibirsk and "Protein contour", St. Petersburg, Russia).

Obtained results were processed by methods of mathematic statistics, using a set of computer programs Microsoft Excel with calculation of significance of differences by Student`s criterion.

STUDY RESULTS AND DISCUSSION OF THEM

According to obtained data, it was established that among subjects with CHC, reactivation phase was detected in 14 (58.3%), latent phase – at 10 (41.7%) of examined children. Reactivation phase was established during detection of anti-HCV IgM and RNA HCV. Latent phase - in children, in blood serum of who anti-HCV IgG was detected.

Distribution analysis of examined children by gender has revealed that among the children with HCV the boys prevailed (65.5%), at that this priority remained in all age groups with maximum high coefficient (71.4%) in

children from 3 to 6 and relative small (60.0%) in groups of 10-12 years. Control group was chosen relative to detected consistency – boys took 66.7% among healthy children. Analysis of age peculiarities of examined children has shown that the number of children with HCV is growing with aging. The most percentage of detectability was observed in subgroups 12-15 years (39.1%) and 15-18 years (20.3%).

Analysis of age peculiarities has shown that the most number of diseased children in reactivation phase (57.1%) was revealed in age of 12-16 years, the smallest number – in age 2-6 years (14.3%). Latent phase of infectious process relatively (70%) was revealed in senior age group, rarely (30%) – in children from 7 to 11 years.

Expressiveness of clinic manifestations in children with HCV examined by us was individual, but in whole they had a tendency to insufficient, slightly expressed complaints (table 1). Astheno-vegetative syndrome was more indicative for children of senior age group (70.8%). Dyspeptic syndrome was observed at the half of examined children (50%) and was indicative for 12-14 year old children. Mixed astheno-vegetative and dyspeptic syndrome was observed even more rarely – in 33.3% of examined children with average age of 13.5 years old. Biliousness was observed most rarely (12.5%) among examined diseased children, and it was indicative for children with average age 9.2 years.

The children, who were in reactivation phase, most often had symptoms of hepatomegaly (71.4% against 50.5 in latent phase), splenomegaly (21.4% against 10.0%), biliousness represented by sclera icterus (71.4% against 40.0%) or skin biliousness (14.3% against 0%). At the same time, such symptoms as palmar erythema, telangiectasia, xanthoma were observed almost with the same frequency as in diseased children in reactivation phase, so in latent phase of disease.

During ultrasonic investigation, we have detected that most of examined subjects did not have fibrosis signs either inactive phase (50.0%), or in latent phase (30%). The children with slightly expressed fibrosis were found either in active phase (35.7%), or in latent phase (30.0%) with almost the same frequency. Moderately expressed or sufficiently expressed fibrosis was distributed almost evenly in the groups of diseased children in latent phase, and in reactivation phase of infection process.

Ultrasonic study was added by study of central and peripheral hemodynamics by Doppler metrics in children with HCV. Introduction of ultrasonic methods of investigation into clinical practice made possible to visualize many parenchymal bodies, including a liver. For example, we have detected increased echoicity of liver, accentuated vascular pattern and extended portal vein during US investigation of children with viral hepatitis. Viral hepatitis is sufficiently distributed disease, which is sometimes hard to diagnose. That is why it is essential to create the program for processing of ultrasonic liver echograms in order to diagnose the hepatitis.

According to obtained results (table 2), change of portal vein diameter is indicative for children with HCV. Increase of this indicator was more sufficient for children in reactivation phase ($p<0.05$). We have not detected the changes of speed indicators of blood flow in examined children.

Table 1

Frequency of clinical syndromes in examined children with HCV

Disease syndromes	Number of diseased, n=24	
	absolute	%
Astheno-vegetative	17	70.8
Dyspeptic	12	50
Mixed:	10	41.7
Astheno-vegetative and dyspeptic		
Arthralgia and dyspeptic	8	33.3
bilious	3	12.5

Table 2

Hemodynamics indicators of children with chronic hepatitis C, depending on phase of infectious progress

Indicator	Children with HCV, n=24		Control group, n=30
	reactivation phase	latent phase	
Diameter, v.v, mm	8,38±0,13*	8,06±0,11*	7,2±0,06
Vmax v.v, m/s	0,20±0,04	0,22±0,06	0,25±0,03
$V_{usual,}$ ml/s	10,5±2,13	12,7±2,08	9,55±2,01

*Note:** - differences are reliable in comparison with indicators of healthy children.

Table 3

Indicators of Doppler sonography in children with HCV, depending on phase of infectious process

Indicator	Children with HCV, n=24		Control group, n=30
	reactivation phase	latent phase	
PI p.a., units	1,64±0,34	1,91±0,23*	1,35 ± 0,1
RI, p.a., units	0,66±0,21	0,46±0,07*	0,64 ± 0,04

*Note:** - differences are reliable in comparison with indicators of healthy children

On our opinion, indicators of blood flow in arterial vessels appeared to be the most informative (Table 3). So, the subjects had increased pulsation index to 11.8% in latent phase, growth of resistivity index took 26.2%. It can be explained by the fact that HCV damages parenchyma and stroma of liver, which is represented by vessel system of body and first reacts to pathologic changes.

Studies of interferon profile in children with HVC have revealed that INF-a concentration exceeded indicators of healthy children. Analysis of INF content, depending on phase of pathologic process has shown a link between these indicators and disease activity: INF-a concentration in subjects with HCV in active phase exceeded control indicators more than 5 times, in latent phase – more than 2 times. Increase of concentration of circulating INF-g, which is a part of immune regulating molecules , which is indicative for Th1 clone of T-lymphocytes, can reflect increase of activity of T-helper cells of first type. It shows that Th1 cytokines take active part in pathologic behavior of liver damage at chronic hepatitis [7, 8].

Therapy of chronic hepatitis C represents big difficulties. According to up-to-date perspectives, prolonged

persistence of viral agents is the base of chronic viral hepatitis progress, which is occurred as result of functional deficiency of factors of cell and humoral immunity, blockage of specific effector reactions and interferongenesis system.

On the basis of above mentioned, the base of etiotropic therapy of HCV is usage of various INF medicine – intracellular proteins, having antiviral and immune modeling signs with specific receptors on cell surface, activating various ferments and genes, which leads to suppression of viral replication, release of RNA virus, its assembling and penetration into the cell.

Decision about antiviral therapy is taken, including all disease parameters: serologic stage and activity, length of disease, accompanying pathology, virological peculiarities if infectious process, including hepatitis, viral loading and other criteria [9, 10].

Taking into account the age, accompanying pathology of some children with HVC examined by us, as well as results obtained in course of examination, relatively low indicators of transaminase activity and saved active production of endogenic interferon, which proved inexpediency of IF-therapy, we decided to choose therapy, which uses endogenic interferon inductors, doing so we have shared opinion of many Russian scientists [11]. Detected violations if intrahepatic hemodynamics in subjects with HCV, probably, can be explained by compensatory mechanisms, directed on improvement of sinusoidal blood flow to support normal functioning of liver. Experimental studies confirmed antioxidant, anti-inflammatory and membrane stabilizing action of Thiotriazolin.

In order to correct revealed violations, we have carried out performance assessment of treatment complex, including antiviral drug Proteflazid, which was subscribed for children within 6 months; and membrane stabilizer Thiotriazolin within 1 month.

Table 4

Changes of interferon profile indicators in children with HCV

Indicator	Healthy children, n=30	Children with HCV, n=24	
		reactivation phase	latent phase
INF-a, pg/ml	6,8±1,3	28,3±3,5 p<0,001	37,6±2,1 p<0,001 p_1 0,001
INF-a, pg/ml	144,9±2,5	183,0±3,1 p<0,001	188,8±3,7 p<0,001 p_1 0,05

Note: p – indicator of difference significance in comparison with indicators of healthy children; p1 - indicator of difference significance in comparison with children, having HVC before treatment (obtained by method of comparison of linked groups).

Table 5

Dynamics of indicators of liver hemodynamics in children with HVC

Indicators	Children with HCV, n=24		Control group, n=30
	reactivation phase	latent phase	
Diameter, v.v, mm	8,18±0,11	7,34±0,09*	7,2±0,06
Vmax v.v, m/s	0,20±0,04	0,27±0,06*	0,25±0,03
$V_{об.}$ ml/s	11,4±2,21	9,71±1,68*	9,55±2,01
PI, units	1,78±0,2	1,5±0,12*	1,35±0,1
IR, units	0,9±0,07	0,81±0,05*	0,72±0,04

Note: * Differences are reliable in comparison with indicators of children before treatment

Application of Proteflazid in complex therapy of children with chronic hepatitis C

T.A. Kruchko, Mohammed M.A. Abdalaal

Flow of chronic hepatitis C at children is characterized by predominating of phase of reactivation (58,3%). The clinical displays were characterized by the complaints of astheno-vegetal (70, 8%), dyspepsia (50%) and icteric (12,5%) syndromes. Studies of central and peripheral hemodynamics showed the changes of diameter of collar vein in both phases (p<0,005). Increase of pulsation index and index of resistance in both phases of infection process. The analysis of maintenance of interferon showed the increase of antiviral interferon b (INF-b) in the phase of reactivation more than in 5 times. Application of Proteflazid and Thiotriazolin membrane stabilizer in complex therapy of children with ChHC was characterized by diminishing of intensity of viral replication in 20,6% cases and increase of concentration of interferon-b in a latent phase, as well as normalization of indexes hemodynamics.

Keywords: *children, chronic hepatitis C, interferon-b and g, Proteflazid.*

REFERENCES

1. Sherlock Sh., Duli J. Disease of liver and biliary tracts: Translation form English M: Medicine; 1999.
2. Uchaikin V.F., Cherednichenko T.V., Pisarev A.G. Assessment of chronic hepatitis progress in children. Russian journal of gastroenterology, hepatology and coloproctology 2000; 2:48-56.
3.Lukyanova O.M., Tarkhovsky M.L., Denisova M.F., Zadorozhia T.D., Babko S.O., Berezenko V.S. Chronic hepatitis in children (issues of pathogenesis and therapy). Theses of reports of 10-th congress of Ukrainian pediatricians. K; 1999: 102
4. Lukyanova O.M., Denisova M.F. Modern problems of children hepatology. Theses of reports of scientific and practical conference of children gastroenterologists of Ukraine. Chernivtsi; 2000: 43-45.
5. Sorinson S.N., Korochkina O.V., Ahdanov Yu.E. etc. Latent phase of chronic hepatitis. Criteria of diagnostics and therapeutic tactics. Viral hepatitis 1999; 1 (5): 17-21.
6. Quin J.W. Aust N.Z.J. Med. 1997; 27: 611-618.
7. Kuramshin D.Kh., Tolokonskaya N.P., Kozhevnikov V.S. etc. Indicators of effector link of immunity and cytokine content in serum in case of viral hepatitis C and combined form of infection C+B. Allergology and immunology 2000; 1 (2):107.
8. Nisevich N.I., Uchaikin V.F., Cherednichenko T.V. etc. Treatment by recombinant b2-interferon of children with chronic hepatitis B and C. Epidemiologic and infectious diseases 1996; 3: 36-39.
9. Malyi V.P., Penkov D.B. Inductors of endogenic interferon in the therapy of acute and chronic forms of viral hepatitis C. Modern infections 2000; 2- 41-45.
10. Reyzis A.R., Nikitina T.S., Drondina A.K. Study of viral hepatitis at a clinical unit for children Epidemiologic and infectious diseases 1999; 3: 46-48.
11. Romantsov M.G. Application of cycloferon in paediatrics. Saint Petersburg; 2000: 15.