DYSPROTEINAEMIA IN VIRAL HEPATITIS

M. Radkov

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The comparison of protein metabolism data with the clinical course of liver diseases enables more successfully to reveal a close relationship between the character of the changes in the course of the disease and the pathological process. Recently, the extensive analysis of the changes of the individual serum protein levels (12) becomes very important. Concerning the acute viral hepatitis (VH) which is still a widespread infectious disease it is to be mentioned that severe alterations of liver protein metabolism commit at the climax of the illness (5, 9, 10). According to Soviet authors (1) there is a decrease of total protein and albumins content but an increase of globulins mainly on the account of gammaglobulin fraction and less expressed of $alpha_1$- and beta-globulin ones in severe VH forms. In our country some systemic investigations of protein spectrum changes were performed mostly with chronic hepatic diseases (2, 3, 4). Many problems related with changes of the serum proteins and antibodies as indicators of the pathological process (its activity, diagnosis, differential diagnosis, and prognosis) which are often necessary in various kinds of jaundice are not yet clarified enough if VH patients and reconvalescent persons are concerned. The practitioner is interested in the following most important and actual questions: when and in which cases VH will have a protracted course, with exacerbations and recidives, with a tendency towards chronification, which are its earliest signs going before the clinical symptoms or even the clinicolaboratory tests. The treatment of dysproteinaemia in both VH and posthepatic conditions is an important stage of the complex therapy. A contemporary practitioner must be aware of these problems, solve them and make correctly his choice between immunosuppressive and immunostimulating drugs.

The aim of the present study was to follow-up the changes of individual serum proteins and immunoglobulins in VH in order to get an exact notion and characteristics of the illness and to correct the present dysproteinaemia. The following determination tasks were to be assigned: 1. Serum concentrations of proteins of synthesis (reflecting mainly the protein-synthetic function of the liver): praealbumin, albumin, transferrin, fibrinogen, fibrin-degradation derivatives D and E, serum cholinesterase, haemopexin, 2. Indexes of the acute stage of the inflammatory process: $alpha_1$-antitrypsin, $alpha_1$-acid glycoprotein, haptoglobin, ceruloplasmin, β_2-glycoprotein I; β_2-glycoprotein II (C_3-activator). 3. Immunoglobulin (IgG, IgM, IgA and IgE) changes as response to antigenic irritation in VH. 4. Changes of certain proteins such as complement C, group-specific protein, C_4, C_9, $alpha_1$-fetoprotein, etc.

Material and methods

The study covered 554 VH patients and 112 reconvalescent persons hospitalized in the Clinic of Infectious Diseases, Higher Institute of Medicine, Varna during the period from 1970 till 1980. They were divided into groups according to the following clinical forms: a) anicteric one — 60 patients (8,88 per cent); b) slightly icteric — 205 ones (30,32 per cent); c) middle-severely icteric — 182 ones (26,92 per cent); d) severely icteric — 95 ones (14,05 per cent); e) dystrophic — 12 ones (1,78 per cent) and f) reconvalescent — 112 ones (18,05 per cent). The following immunochemical methods based on the immunoprecipitation reaction were used to study serum proteins in VH: quantitative determination of serum proteins after Mancini, immunoelectrophoresis, bilateral immunodiffusion, electrophoretical immunoprecipitation, rosette-test for T-cell determination. The data were statistically processed by using the variation and graphic analysis. Sera of 300 healthy blood donors from Varna city and the district of Varna were used as controls.

Results and discussion

Our investigations of the quantitative changes of individual proteins and immunoglobulins in VH patients and former VH cases showed a differently expres-

Table 1

Comparison between the mean levels of certain individual serum proteins in VH patients positive for hepatitis B and negative for the same disease

Protein	Kind of hepatitis	$\bar{x}$	σ	m_x	C (%)	t	$F_{(t)}$
Albumin	hepatitis A	3327	225	290	6,76	1,730	>0,1
	hepatitis B	2827	1591	289	56,34		
	controls	3998	181	30	4,55		
Transferrin	hepatitis A	271,80	211,2	21,55	79,99	0,814	>0,5
	hepatitis B	194,24	92,84	16,16	47,79		
	controls	272,82	44,67	8,44	16,42		
Fibr nogen	hepatitis A	230,78	100,3	10,23	43,46	0,687	>0,5
	hepatitis B	219,42	74,97	13,04	34,16		
	controls	393,30	27,39	9,13	6,96		
α_1-Anti-	hepatitis A	278,26	117,3	11,76	42,05	0,170	>0,9
trypsin	hepatitis B	258,10	103,9	17,08	40,25		
	controls	290,83	27,24	8,61	9,36		
Cerulo-	hepatitis A	8,49	5,84	0,54	68,88	0,115	>0,9
lasmin	hepatitis B	7,37	4,58	0,79	62,17		
	controls	17,95	7,75	2,23	43,18		
α_2-macro-	hepatitis A	244,58	81,26	13,45	33,22	1,606	>0,2
globulin	hepatitis B	274,55	86,75	12,87	31,45		
	controls	257,32	42,85	8,09	16,67		
Haptoglo-	hepatitis A	164,05	115,8	12,94	70,58	2,098	<0,05
bin	hepatitis B	191,81	116,2	2,86	60,58		
	controls	172,50	40,5	11,69	32,47		
β_2-glycopro-	hepatitis A	11,97	2,22	0,21	18,54	0,791	>0,5
tein I	hepatitis B	12,69	5,62	0,88	44,28		
	controls	7,56	1,60	0,46	21,22		
C_3-activa-	hepatitis A	9,02	4,87	0,53	54,05	0,935	>0,5
tor	hepatitis B	9,97	6,38	1,18	64,00		
	controls	12,19	2,34	0,67	19,21		

sed dysproteinaemia depending on the clinical form and the stage of the disease (table 1). Mean protein levels reflecting mainly liver capacity for protein synthesis decreased progressively attending the hepatic damage (fig. 1). This was established first for prealbumin that was reduced in 93,2 per cent of the cases at the

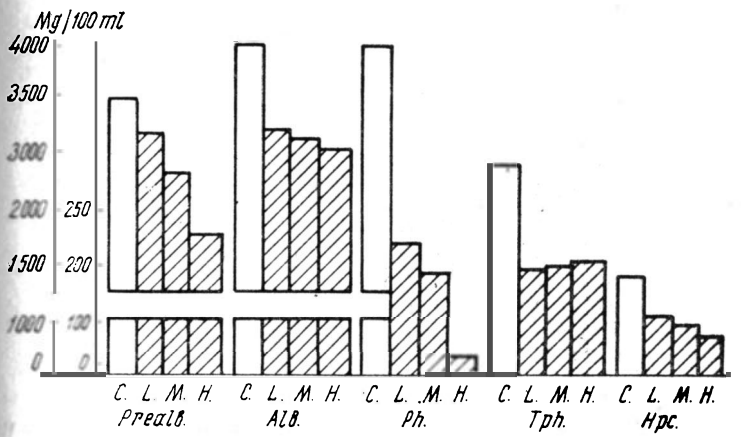

Fig. 1. Changes of serum proteins reflecting predominantly protein-synthesis function of the liver in different clinical forms of viral hepatitis

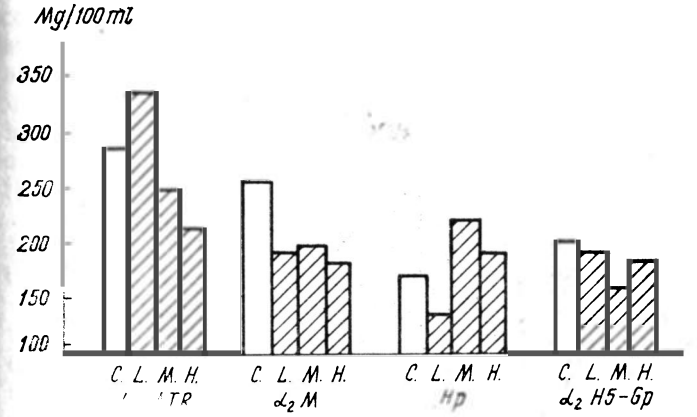

Fig. 2. Changes of serum proteins — indexes of the acute phase of the inflammatory process in different clinical forms of viral hepatitis

onset of the disease. Albumin was also significantly reduced. Transferrin was statistically significantly decreased in any clinical forms ($p < 0,01$) (8). This fact is a true sign for liver lesions in VH. Haemopexin was also significantly diminished. This protein is still insufficiently studied in our country. Its changes attest the disturbances of liver protein-synthetic functions. Fibrinogen levels are so sensitive that together with other coagulation tests they can be used as a reliable criterion for VH prognosis. The stronger the acute massive liver necrosis and cytolysis, the lower the fibrinogen levels.

The greatest part of the individual proteins of the second group decreased, too (i. e. alpha$_1$-antitrypsin diminished in middle-severe and severe VH forms but increased in mild cases (fig. 2). It could be due to glycocorticosteroid suppres-

sion administered to most patients because of total intoxication and hyperbilirubinaemia. Alpha$_2$-macroglobulin, one of the "heavy proteins" was reduced in any patients. The differences in single cases were insignificant. Haptoglobin decrease could be explained with the diminished liver protein synthesis in VH.

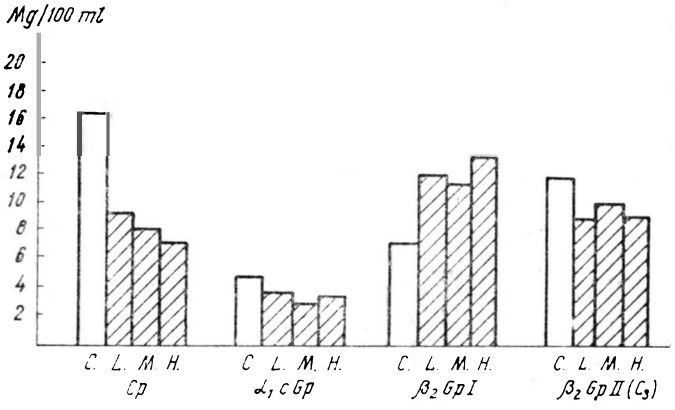

Fig. 3. Changes of serum proteins during the acute inflammatory response in different forms of viral hepatitis

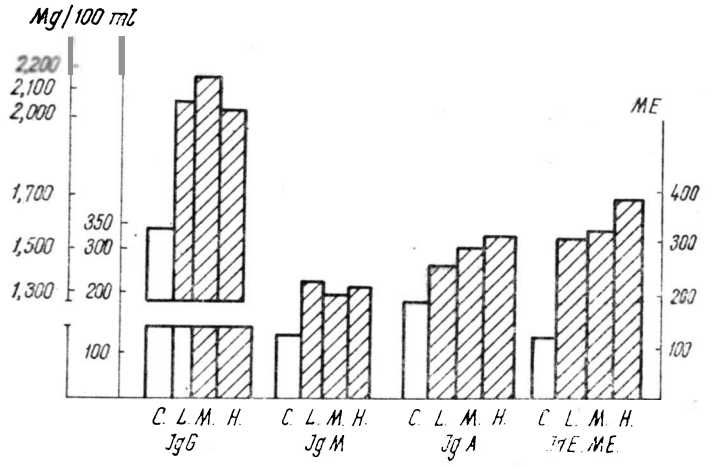

Fig. 4. Changes of serum immunoglobulins in different forms of viral hepatitis

Because of its short half-life its level can be used as a good indicator for liver functional state concerning protein synthesis. The constant tendency towards ceruloplasmin reduction is strongly related with the seriousness of the illness. Any other proteins of the glycoprotein group were also decreased (fig. 3).

Concerning the characteristics of VH clinical course the dynamic follow-up of the serum immunoglobulins revealed the clinico-laboratory gravity to be attended by a sharply expressed IgA increase (6) (fig. 4). During the first 2—3 weeks after the onset of the illness there was a maximal IgM increase as an evidence for liver cytolysis. At the end of the icteric period IgG started an increase as a sign of fibrous-proliferative processes in liver parenchyma. In general, VH is characte-

rized with an expressed gammopathy (a rising polyclonal immune response to the antigen irritation) presented clearliest in the efferent stage of humoral immune response. Dysproteinaemia is best expressed in severe and dystrophic VH forms (7) in which there is a strong reduction of synthesis proteins, of some immune

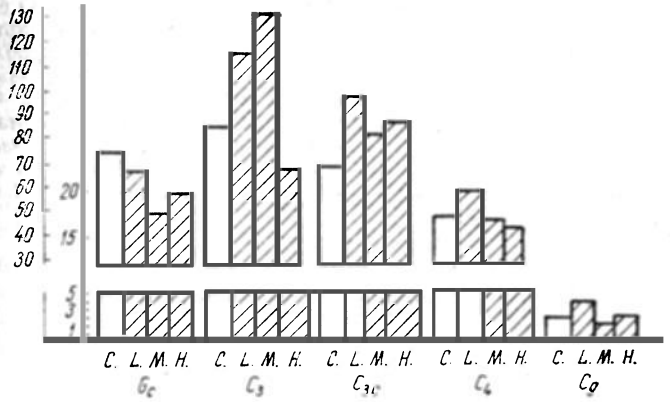

Fig. 5. Changes of complement components in different forms of viral hepatitis

esponse ones, and of three main classes of immunoproteins (fig. 5). Glycocorticoid treatment of VH causes an expressed negative effect on protein metabolism and plasma protein synthesis suppression, i. g. prealbumin, albumin, transferrin, $alpha_1$-antitrypsin, ceruloplasmin and $alpha_2$-macroglobulin. Primary humoral immune response is also strongly inhibited and antibody production (mainly IgG and IgM) is markedly reduced. The presence and persistence of HBsAg induces a reduction of the proteins of the three groups, too. The diagnostic significance of the individual proteins and immunoglobulins can be summarized as follows:

They enable the differentiation between the A and B VH-forms by means of IgM dynamic follow-up, especially with posttransfusion hepatitis as well as between the acute VH and chronic hepatitis where IgG levels are significantly higher.

Both IgG and IgM are in normal ranges or slightly elevated only with cholestatic VH forms and extrahepatic jaundices. The rapid and extreme increase of the three classes of immunoglobulins indicates the risk of an acute massive hepatic necrosis followed by a hepatic coma. The low levels of proteins of synthesis, especially of fibrinogen, give an evidence of a dangerous haemorrhagic diathesis in the course of the disease. IgM persistence in reconvalescent patients shows the danger of recidives. Serum proteins and immunoglobulins determination provides a better and more detailed and valuable information than proteinogram and colloid-stability hepatic tests for treating physicians. Various constellations of individual serum proteins and immunoglobulins are possible and can be applied for the evaluation of the functional state of the liver in VH.

Bulgarian hydrolysate "Hydroprot'' application (11) in the treatment of VH patients influences favourably the present dysproteinaemia by means of increasing the serum levels of the proteins of the first group (albumin, transferrin, haemopexin), of some ones of the second group ($alpha_2$-macroglobulin, $alpha_1$-easily sedimentating glycoprotein, group-specific protein, C_3-activator), etc. There is a simultaneous reduction of the serum level of the gamma-globulin fraction mainly on the account of IgG.

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ДИСПРОТЕИНЕМИЯ ПРИ ВИРУСНОМ ГЕПАТИТЕ

М. Радков

РЕЗЮМЕ

Для изучения изменений белкового обмена и диспротеинемии при остром вирусном гепатите было исследовано 554 больных и 112 выздаравливающих, лечившихся в клинике инфекционных болезней в Варне с 1970 по 1980 г. г. Иммунохимические исследования количественных изменений индивидуальных сывороточных белков и исследования антител трех основных классов иммуноглобулинов показывают значительное уменьшение белков, что связано с белок-синтезирующей способностью печени (преальбумин, альбумин, трансферин, фибриноген, гемопексин). Большая часть белков в острой фазе воспалительного ответа тоже уменьшается (альфа$_1$-антрипсин, альфа$_2$-макроглобин, гаптоглобин, церулоплазмин). Устанавливается повышение стоимости ИгА и нарастание тяжести заболевания.

Автором подчеркивается факт, что определение сывороточных белков и иммуноглобулинов дает детальную и ценную информацию о состоянии печени при заболевании гепатитом по сравнению с протеинограммой и коллоидостабилитетными печеночными пробами.