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DELTA INFECTION IN CHILDREN WITH CHRONIC VIRAL HEPATITIS B*

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SUMMARY: Makmudov OS, Inoyatova FI, Kadirov BA, Abdumadjidova SU. (Scientific Research Institute of Pediatrics of the Republic of Uzbekistan, Tashkent, Uzbekistan). Delta infection in children with chronic viral hepatitis B. Turk J Pediatr 1997; 39: 75-80.

The incidence and clinical features of chronic viral hepatitis B associated with the delta infection were studied in 300 children between one and 14 years in age. Anti-delta was found in 42 (14%) of 300 children with chronic viral hepatitis B, predominantly in patients with chronic active hepatitis who had anti-HBe; exacerbations were found in 11 of 12 children with anti-delta, but in only four of 12 children without these antibodies. These findings confirm the assumption that the process of exacerbation in patients with chronic active hepatitis and anti-HBe may be related to super-infection induced by the delta virus. *Key words: chronic viral hepatitis, delta virus infection, HBsAg carriers, children.*

A number of investigators consider the delta virus to be an important etiological factor in the chronicity of viral hepatitis[1, 2]. However, the causes of chronicity of the disease in delta virus infection remain unknown. It is evident, at least, that the association of the delta virus and the HBsAg carrier state, or chronic viral hepatitis B, often leads to the development of chronic active hepatitis delta[3, 4]. As a matter of fact, chronic hepatitis delta is as a rule, a chronic viral process of mixed etiology (HB- and HC- viral), with leading activity of the delta virus. The determination of antibodies to the delta-antigen in the blood of patients with chronic hepatitis D is laboratory confirmation of the presence of delta infection, and a high titer of antibodies to the IgM-type delta-antigen suggests a chronic process[5].

The delta infection is a widely-distributed disease, particularly in regions with a large number of HBsAg-carriers, such as Moldavia in Central Asia[6]. So-called chronic hepatitis B, especially chronic active hepatitis B, appears to be chronic hepatitis D in at least 60 percent of cases[7]. A higher incidence of the delta infection has been documented in patients with chronic active hepatitis and liver cirrhosis[8, 9]. There have been few reports devoted to the delta infection in children[10]. The aim of this work was to identify the peculiarities of delta infection development in children with chronic viral hepatitis B.

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Material and Methods

In the present investigation, the incidence and clinical features of chronic viral hepatitis B associated with the delta infection were studied in 300 children between one and 14 years in age.

The diagnosis of chronic persistent hepatitis and chronic active hepatitis was made on the basis of the serological markers of hepatitis B virus (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc) and anti-delta using radioimmunoassay and enzyme multiple immunoassay (Abbott, USA). Diagnosis was based on clinico-biochemical and immunologic investigations, ultrasound examination, scanning and liver biopsy. Histological investigation of liver biopsy specimens was performed in children with chronic viral hepatitis B; in 98 percent of cases, morphological changes were found in the liver, which is characteristic of chronic active hepatitis and chronic persistent hepatitis.

Statistical analyses were performed using student's t-test.

Results

Anti-delta was found in 95 (31.7%) of 300 children with chronic viral hepatitis B, predominantly in patients with chronic active hepatitis. The antibodies were present in 73 of 159 children with chronic active hepatitis and in 22 of 141 patients with chronic persistent hepatitis. In chronic active hepatitis, anti-delta was found more frequently ($p < 0.01$) in patients with constant activity than in those with alternating periods of exacerbation and remission. Among the patients with chronic viral hepatitis B in association with the delta infection, serum samples revealed high titers of anti-delta in chronic active hepatitis and low titers in chronic persistent hepatitis.

Analysis of patients' health histories revealed that there were no differences in the frequency of intravenous injections or dental extractions in children with and without anti-delta. A history of blood transfusion was noted more frequently in children whose serum samples were positive for anti-delta than in without anti-delta. Jaundice was also more common in patients with anti-delta ($p < 0.01$). This reconfirms the fact that super-infection induced by the delta virus is one of the causes of exacerbation in chronic carriers of hepatitis B virus.

It should be noted that most (80.9%) of the children with chronic viral hepatitis B in association with the delta-infection had acute viral hepatitis B in the past. The course of disease was undulating and had some peculiarities. The initial diagnosis was typically a mild form of viral hepatitis B with HBs-antigenemia. The first "peak" of disease was followed by remission lasting for four weeks to two months, during which period the patient's health was good, jaundice was absent and only moderate hepatomegaly was present; however, HBsAg continued to be noted in all of the children's serum. After remission, patients' conditions

worsened and jaundice reappeared. The "second wave" of hepatitis was severe with more marked intoxication and jaundice. The remaining patients with chronic viral hepatitis B had no previous manifested form of disease but were diagnosed after clinico-laboratory investigations.

The prospective study on the time of diagnosis of chronic disease after acute viral hepatitis revealed that of the 73 children from the group with chronic active hepatitis D, diagnosis was established within one year in 56.2 percent of cases, after two to three years 28.8 percent, and later in 15.0 percent of children. These figures may suggest that delta infection may lead to a chronic process in earlier phases of the disease.

The incidence of anti-delta increased with the age of patients; i.e., these antibodies were found more frequently in children older than seven years than in children one to three years in age. This evidence, obviously, may be explained by the correlation between the age of patients and the duration of disease, because many patients had been contaminated by the hepatitis B virus in early childhood.

The examination of children for identification of hepatitis B virus markers revealed a high rate of HBsAg positivity in all forms of disease (Table I). Anti HBs was found

Table I: Rate of Determination of Hepatitis B Serologic Markers and Delta Infection in children with Different Forms of Chronic Liver Disorders

	Nosologic forms and disease activity						
	Chronic active hepatitis				Chronic persistent hepatitis		
Virus markers (abs./%)	Total (n: 89)	High degree (n: 31)	Moderate degree (n: 27)	Mild degree (n: 31)	Total (n: 35)	Active phase (n: 27)	Passive phase (n: 8)
HBsAg	79/88.8	28/90.3	24/88.8	27/87.1	34/97.1	26/96.3	8/100.0
Anti-HBs	9/10.3	3/9.7	2/7.4	4/12.9	2/5.7	2/74	0/0.0
HBeAg	15/16.9	4/12.9	5/18.5	6/19.3	3/8.6	3/11.1	0/0.0
Anti-HBe	33/37.1	6/19.4	11/40.7	16/51.6	13/37.1	11/40.7	2/5
Anti-delta	73/82.0	29/93.5	24/88.8	20/64.5	22/62.9	22/81.5	0/0.0
Anti-HBc	61/68.5	15/48.4	22/81.5	24/77.4	18/51.4	17/63.0	1/12.5

three times more often in the group of children with chronic active hepatitis than in patients with chronic persistent hepatitis ($p < 0.05$). Infectivity and virulence markers (HBeAg) were found 1.7 times more frequently in cases of chronic active hepatitis than in chronic persistent hepatitis. This may indicate that continuous viral replication is more marked in chronic active hepatitis. There was a considerable frequency of anti-HBe, anti-HBc, and anti-D determination in both forms of the disease. Anti-D was noted in 82.0 percent of chronic active hepatitis cases, which may be an indirect

indication of the severity of the pathological process in children from this group. The rate of anti-D determination during chronic persistent hepatitis was high, which may be related to the predominance of children in the active phase of the disease in this group. During the development of disease activity, an increase in the frequency of anti-D determination was found in the group of children with chronic active hepatitis.

Discussion

Some authors explain the clinico-laboratory exacerbation in patients with chronic viral hepatitis B and the presence of anti-HBe by the accompanying delta infection[11, 12]. Taking into consideration the possible specific effect of virus D on hepatitis B virus replication, we evaluated the rate of determination of the system HBV antigen-antibody in relation to the presence of anti-D (Table II). The less frequent finding of anti-HBs in patients with anti-D and chronic active hepatitis ($p > 0.05$) may be explained by the fact that virus D used the hepatitis B virus surface antigen for its replication and reduced the synthesis of the proper antibodies. Besides, anti-HBs might be connected to circulating immune complexes in blood serum. At the same time anti-HBe and anti-HBc were found more frequently in D-positive forms with the presence of anti-D.

Table II: Rate of Determination of Hepatitis B Virus Markers in Children with Different Forms of Chronic Liver Disorders in Relation to Anti - D Presence

	Nosologic forms with (+) or without (-) anti - D					
	Chronic active hepatitis		Chronic persistent hepatitis		Total	
Hepatitis B virus markers (abs./%)	+ (n: 73)	- (n: 16)	+ (n: 22)	- (n: 13)	+ (n: 95)	- (n: 29)
HBsAg	65/89.0	13/81.3	21/95.5	11/84.7	86/90.5	24/82.8
Anti-HBs	7/9.6	3/18.8	2/9.1	1/7.7	9/9.4	4/13.8
HBeAg	13/17.8	4/25	3/13.6	2/15.4	16/16.8	6/20.7
Anti-HBe	29/39.7	6/37.5	12/54.5	3/23.1	41/43.2	9/31.0
Anti-HBc	54/74.0	6/37.5	16/72.7	4/30.8	70/73.7	10/34.5

Clinical exacerbations in children with chronic active hepatitis associated with delta infection include the development of jaundice ($p < 0.001$); marked extrahepatic features such as large vascular "asters" on the face, back, and shoulders; erythema; increased subcutaneous venous pattern on the breast and abdominal wall; and considerable enlargement of the liver. Marked liver induration is a specific sign of chronic active hepatitis D. Enlarged spleen, sometimes exceeding the liver in size, was found in all children. In chronic active hepatitis

without anti-delta, these features were observed less frequently; exacerbations were diagnosed predominantly with deteriorating biochemical findings. The obtained results were confirmed by physical findings: intoxication, extrahepatic features, jaundice, and hemorrhagic manifestations such as nasal hemorrhage (observed 1.4-1.6 times more often in chronic active hepatitis associated with delta-infection). During decompensation of the process in chronic active hepatitis D, we observed ascites and signs of subacute liver dystrophy (three patients). These findings were absent in cases of chronic active hepatitis B.

The course of disease tended to fluctuate. The above-mentioned clinical signs were most notable during the exacerbation of disease and were diminished in the period of remission. This alternation of exacerbation and remission is characteristic of chronic active hepatitis D. The histological picture of the liver in chronic active hepatitis D was characterized by a more severe pathological process in both the parenchyma and the portal tract, while chronic active hepatitis B was expressed by more marked intralobular infiltration, fibrosis of the portal tracts, and an increase in parenchymal lymphocytes and macrophages.

In chronic persistent hepatitis, the clinical features of intoxication, jaundice and hemorrhagic syndrome were less marked. The exposed changes were more characteristic for anti-delta, chronic persistent hepatitis[13, 14]. An increase in liver size more than three cm below the costal margin was found two times more often, and the presence of an enlarged spleen 2.5 times more often in children with anti-delta chronic persistent hepatitis. The reliable differences were identified in liver function tests in chronic active hepatitis with and without anti-delta. Chronic active hepatitis in children with anti-delta is associated with more profound features of hepato-cellular failure, characterized by the following main syndromes: mesenchymal inflammation, cytolysis and disturbance of protein synthesis function[14, 15]. Functional liver biopsy mainly identified findings of mesenchymal inflammatory syndrome, showing a two-fold increase in the gammaglobulin level. Prolonged cholestasis was noted in these children, accompanied by a high level of bilirubin due to both conjugated and unconjugated bilirubin. Different levels of cytoplasmic enzymes (ALT, AST; $p < 0.001$) were determined in chronic persistent hepatitis with and without anti-delta; their activity in chronic persistent hepatitis with anti-delta was 2.3 and 2.1 times higher, respectively, than without anti-delta.

The results of the investigation show a high incidence of delta-infection among children with chronic active hepatitis. A correlation was found between the frequency of anti-delta occurrence, the duration of the illness, and the presence of exacerbations in the dynamics of disease.

Delta-infection is characterized by a more rapid formation of a chronic process after acute viral hepatitis. The clinical course of D-infection includes frequent and striking exacerbations. It is necessary to take into consideration all these patterns in order to clarify the prognosis of the disease and to individualize treatment.

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