VIROLOGY

Systemic Endotoxemia during Chronic Viral Hepatitis

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Incidence and severity of systemic endotoxemia in patients with chronic viral hepatitis B and C were studied using the limulus test. Healthy subjects and patients with acute viral hepatitis B and C comprised reference groups. The incidence of "physiological" systemic endotoxemia in healthy subjects was 31.3%, while in chronic hepatitis systemic endotoxemia was found in 69-84% patients and it was more severe in this case. A significant correlation was revealed between systemic endotoxemia with virus replication and the degree of basic clinical and laboratory signs in patients with chronic viral hepatitis B.

Key Words: *endotoxin; systemic endotoxemia; chronic viral hepatitis B and C; pathogenesis*

Lipopolysaccharides (endotoxins) of gram-negative bacteria attract not much attention as an important pathogenetic factor, because pathophysiologic phenomena caused by endotoxins (asthenia, anorexia, cholestasis, leukopenia, fever, and body weight loss) coincide with typical symptoms of chronic liver diseases [1,4]. Even under normal physiological conditions, endotoxins from the intestine via portal blood flow enter liver, the first and major organ of their elimination [5]. Evidently, chronic damage to hepatocytes during chronic viral hepatites impairs barrier function of the liver and leads to systemic endotoxemia (SET). This phenomenon is observed in hepatic cirrhoses of diverse ethiology and in liver alcoholic disease [3,7]. It is widely known that the complex of anti-endotoxin factors (anti-endotoxin antibodies, HDL, albumins, and the cell acceptors such as neutrophils, platelets, and eosinophils) is involved in pathogenetic "conflict" during chronic viral hepatites [6].

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Our aim was diagnosis of SET in patients with chronic viral hepatites B and C (CVHB and CVHC, respectively) and evaluation of its correlations with clinical peculiarities of the disease and basic clinical and laboratory signs of CVHB and CVHC.

MATERIALS AND METHODS

We examined 68 patients wit CVHB and 148 patients with CVHC (61.2% males, 73.6% subjects aged 16-30 years). Healthy subjects (n=32), patients with progressive acute viral hepatitis B (n=50), and patients with acute viral hepatitis C during convalescence (n=35) were also examined.

Endotoxin was determined by the limulus-test using a E-Toxate kit (Sigma) [2]. The diagnosis was verified and activity of the pathological process was evaluated using clinical, epidemiological, and routine biochemical and serological (HbsAg, HbeAg, aHBcor-IgM, aHCV, aHCV-IgM) tests and polymerase chain reaction (PCR) for hepatitis B virus DNA and hepatitis C virus RNA in semiquantitative mode.

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RESULTS

Physiological SET was found in 10 (31.25%) healthy subjects, it varied from 0.0001 to 0.163 endotoxin units per 1 μl (0.042±0.012 EU/μl).

In patients with viral hepatitis SET was diagnosed more often than in healthy subjects (Table 1).

The severity of SET did not correlate with its incidence. CVHB was characterized by more severe SET, although endotoxin was more often detected in the blood of CVHC patients (Table 1).

Activity of the infectious process during viral hepatites is currently evaluated by measuring viral load using PCR. We showed that the absence of hepatitis B virus DNA or hepatitis C virus RNA was associated with lower incidence and lower concentrations of endotoxin in the blood. In CVHB patients this dependence was significant. Endotoxin was not detected in CVHB patients with negative PCR test, while 70.97% patients with positive test had SET (2.989±1.232 EU/μl). Maximum incidence (100%) and severity (7.256±4.434 EU/μl) of SET in CVHB patients was observed during active viral replication (+++++).

In most examined patients, chronic viral hepatitis was in the latent phase with poorly symptomatic or asymptomatic clinical presentation. However, the observed cases of enzymatic or clinical exacerbation as well as combination of clinical manifestations and biochemical signs of cytolysis attested to a correlation between SET and exacerbation of the disease.

In CVHB patients SET was clearly associated with clinical and biochemical exacerbations and with the stage characterized by elevation of cytolytic enzymes (alanine and aspartate aminotransferase). In CVHC patients SET was observed both during remission (90.4%) and acute clinical period.

It was interesting to find out whether cytolysis (detected by the level of alanine aminotransferase) was caused by SET. We found that the 3-fold increase in activity of this enzyme during CVHB (in comparison with healthy subjects) was associated with higher incidence (80 *vs*. 60%, $p<0.05$) and severity (4.01±1.99 *vs.* 0.100±0.026 EU/μl) of SET. By contrast, no such correlation was found in patients with CVHC.

There can be a relationship between serum level of endotoxin and cholestasis syndrome. In our study none of the examined patients had pronounced cholestasis, which usually attests to reactivation of the infectious process. However, even in the cases with insignificant increase in total bilirubin (up to 2.5-fold in comparison with healthy subjects), CVHB m patients had pronounced SET (Table 2). Endotoxin was more often detected in CVHC patients without cholestasis compared to CVHB patients with hyperbilirubinemia (Table 2).

TABLE 1. Incidence (%) and Severity (EU/μl (*M*±*m*) of SET in Healthy Subjects and Patients with Viral Hepatitis

Group	Incidence	Degree
Healthy subjects (*n*=32)	31.25	0.042±0.012
Acute hepatitis		
B (*n*=33)	81.25*	1.00±0.41^{+}
C (*n*=21)	80.0*	0.30±0.09*$^{++}$
CVHB (*n*=43)	69.0*	3.02±0.66*
CVHC (*n*=83)	83.8*$^{++}$	0.99±0.25*$^{++}$

Note. *$p<0.05$ compared to healthy subjects; $^{+}p<0.01$, $^{++}p<0.05$ compared to patients with CVHB.

Intoxication is usually considered as basic syndrome caused by enhanced concentration of serum endotoxin. In most patients with viral hepatitis, intoxication syndrome was not accompanied by fever, so it is difficult to obtain objective clinical presentation in such cases. However, serum endotoxin with increasing leukocytic intoxication index in CVHB patients.

The data obtained indicate that SET is a typical pathophysiologic phenomenon observed during CVHB and CVHC. Significant correlation between SET and the severity of basic clinical and biochemical syndromes in CVHB patients attests to the involvement of endotoxin in the pathogenesis of intoxication syndromes, cytolysis, and cholestasis, as well as in the formation of clinical picture of CVHB. It is corroborated by correlation between the degree and incidence of SET, on the one side, and activity of virus replication and the number of DNA copies of hepatitis virus B in serum, on the other side.

There were no direct interrelations between SET, major clinical and biochemical syndromes of the disease,

TABLE 2. Incidence (%) and Severity (EU/μl, *M*±*m*) of SET in CVHB and CVHC Patients with Different Bilirubin Levels

Patients	Total bilirubin level, μM/liter	
	<20.5	>20.5
CVHB (*n*=43)		
incidence	85.5	100
severity	1.66±0.79	8.03±3.01*$^{+}$
CVHC (*n*=83)		
incidence	84.1	28.6^{++}
severity	0.462±0.218*	0.103±0.09*

Note. *$p<0.05$ compared to healthy subjects (Table 1); $^{+}p<0.01$, $^{++}p<0.05$ compared to the corresponding parameter at total bilirubin level <20.5 μM/l.

and manifestations of active infectious process in CVHC patients. This probably reflects peculiarities of immunopathogenesis of CVHC, which is characterized by insufficient immune response determining chronical course of the disease in many cases. In many patients with acute viral hepatitis C SET was diagnosed only during convalescence; it was more often found in patients with progressive course of acute viral hepatitis B.

It should be noted that limulus test widely used in experimental studies, is now recommended for pyrogen detection in various medical preparations, but not in the blood (because of possible nonspecific reactions). Nevertheless, the regularities found in this study are determined by endotoxin, rather than by some nonspecific factors.

The described phenomena and regularities provide new insight into the complex of interaction of macroorganism, microflora (the endogenous producer of endotoxin), and infectious agents and into diagnostic and therapeutic approaches to CVHB and CVHC.

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