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CLINICAL IMPORTANCE OF ASSESSMENT OF HBsAg/IgM COMPLEXES IN CHRONIC HEPATITIS B

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Summary. – In serum of patients with chronic hepatitis B (HB) in the stage of active viral replication HBsAg/IgM complexes were detected. Using a commercial kit AU-IGM-K Sorin Biomedica HBsAg/IgM complexes in 136 patients with chronic HB and cirrhosis of the liver were examined, incl. 89 men, 42 women and 5 children, mean age 48 ± 17 years. With regard to the results of the serological examination for HB virus (HBV) markers the results in 54 patients with positive HBeAg and HBsAg in serum (group 1) were compared with 68 patients with positive HBsAg only (group 2) and with 14 patients with positive antibodies against HBV or unrelated to HBV (group 3). The mean positivity index of HBsAg/IgM complexes in group 1, 2 and 3 was 9.89, 1.85 and 0.50, respectively. The results suggest a significant predominance of HBsAg/IgM complexes in patients during the stage of active viral replication with positive HBeAg in serum, as compared with patients without HBeAg ($p = 0.001$) and the control group ($p = 0.001$). A similar significant difference between groups was found as regards to ALT and AST activities. We conclude that in patients with chronic HBeAg positive hepatitis and a moderately elevated transaminase activity usually also HBsAg/IgM complexes, which are closely correlated with HBeAg, are positive.

Key words: HBsAg/IgM complexes; chronic hepatitis B

Introduction

In acute viral hepatitis specific and non-specific immune complexes are formed which circulate in the blood stream. They are formed by specific antigens and antibodies, albumin and immunoglobulins. During the onset of acute viral HB specific HBsAg/IgM complexes are formed which contain receptors for polymerized human serum albumin, Dane particles and viral DNA polymerase. The link between HBsAg and IgM is a bridge from polymerized human serum albumin (Sansonno *et al.*, 1985). In the complexes also pre-S2

were detected, but no anti-HBs were found (Grangeot-Keros *et al.*, 1988).

In acute viral HB HBsAg/IgM complexes in high titers are present and if the immune response to HBV is normal they disappear within four weeks (Caredda *et al.*, 1982). Seroconversion of HBeAg to anti-HBe precedes the disappearance of complexes from serum. If, however, the complexes do not disappear from serum within 5 weeks after onset of the disease, this is one of the first indications of the incipient chronic evolution of the disease and at the time also HBeAg and HBsAg persist in serum (Caredda *et al.*, 1982; Camareno *et al.*, 1991).

Later evidence was provided that specific HBsAg/IgM complexes are found in serum also in chronic HB, cirrhosis of the liver and hepatocellular carcinoma in patients where HBsAg and HBeAg are present in serum, while in sera without HBeAg they are less frequent (Coursaget *et al.*, 1986).

In the present work we tried to assess the relationship of HBsAg/IgM complexes to HBeAg in patients with chronic HB.

Table 1. Histological findings in patients' groups

Group	N	CI	CAH	CPH	Non-specific changes
1	54	17	34	0	3
2	68	19	17	12	20
3	14	6	6	2	0
Total	136	42	57	14	23

CI - cirrhosis; CAH - chronic active hepatitis; CPH - chronic persistent hepatitis; non-specific changes - chronic carrier state, hyperbilirubinaemia, fibrosis, steatosis, resolving hepatitis

Table 2. Mean values of HBsAg/IgM complexes and mean ALT and AST activities in patients' groups

Group	HBsAg/IgM complexes (IP)	ALT (μkat/l)	AST (μkat/l)
1	9.89±5.23	3.34±2.66	1.26±0.80
2	1.85±1.85	1.21±2.33	0.56±0.57
3	0.50±0.29	1.16±0.76	0.62±0.35

Normal values for both ALT and AST are lower than 0.5 μkat/l.

Materials and Methods

Patients. In 1986–1987 we examined HBsAg/IgM complexes in 136 patients with chronic hepatitis B and cirrhosis. The group comprised 89 men, 42 women and 5 children, mean age 48 ± 17 years (range 9–81 years). All patients were followed up for prolonged periods and were subjected to the usual biochemical examinations.

Based on the results of RIA, the patients were divided into three groups: 54 patients suffered from chronic hepatitis B in the stage of active viral replication (positive HBsAg and HBeAg in serum, group 1); 68 patients were after HBeAg seroconversion but HBsAg was still positive (group 2); 14 patients had positive antibodies against HBV or were unrelated to HBV and served as controls (group 3).

In the majority of patients followed up on a long-term basis the histological examination of the liver, based on blind liver biopsy by a Menghini needle was carried out. The data are listed in Table 1.

Serological examination. In all patients blood specimens were tested for HBsAg, HBeAg, anti-HBe, anti-HBc and anti-HBs by solid-phase RIA (Abbott Laboratories), and in some patients the HBeAg/anti-HBe system was tested by commercial RIA (Sorin Biomedica).

HBsAg/IgM complexes were detected in all patients using commercial RIA (AU-IGM-K Sorin Biomedica) according to the manufacturer's instructions. The results were expressed as positivity index (IP): under 1.0 negative, above 1.0 positive.

Statistical analysis. Arithmetic mean, standard deviation, variation and Chi-square were used for statistical comparisons.

Results

The mean IP of HBsAg/IgM complexes, the mean ALT and AST activity in patients' groups is presented in Table 2. From the results ensues that in group 1 there was a significantly higher IP of HBsAg/IgM complexes and ALT and

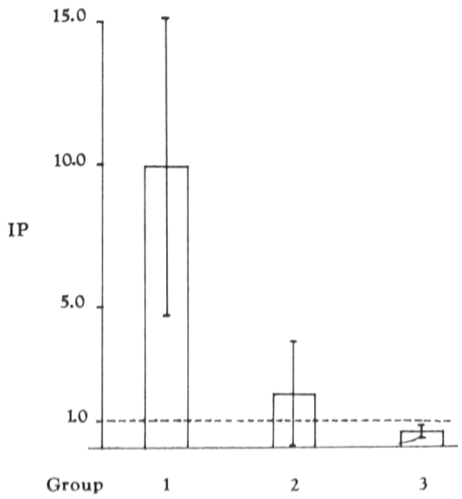

Fig. 1
Positivity index of HBsAg/IgM complexes in patients' groups
IP: positivity index

AST activity than in groups 2 and 3 ($p = 0.001$ for all three indicators).

In group 1 there was only one patient with a very low IP of 1.06 (i.e. marginal positivity, but he could have been also negative), the others were clearly positive with an IP of at least 3.0. On the other hand, in group 2 two patients had an IP above 3.0 but in 25 patients the IP was negative (less than 1.0).

The predominance of HBsAg/IgM complexes in replicative stage of chronic hepatitis B is obvious from Fig. 1.

The results suggest that in patients with chronic HB in the stage of active viral replication serum HBeAg correlates significantly with circulating immune HBsAg/IgM complexes in contrary to patients without HBeAg where these complexes are usually negative. Positive immune complexes HBsAg/IgM in patients with chronic HB are another serological marker of probable active viral replication.

Discussion

The prognosis of acute viral HB can be assessed in every patient within 2–4 weeks after the onset of disease, based on the titer of HBsAg/IgM complexes. A chronic course of hepatitis can be predicted already after 2 weeks with a 82 % probability and after 4 weeks with an almost 99 % probability (Frisch-Niggemeyer *et al.*, 1984).

A favourable prognosis of HB is suggested by early disappearance of HBV DNA, disappearance of HBeAg, subsequent drop of HBsAg and disappearance of HBsAg/IgM complexes from serum (Hoffmann *et al.*, 1988). It is therefore better to evaluate several prognostic indicators to establish the final prognosis.

In chronic HB in the stage of active viral replication specific HBsAg/IgM complexes were found in 53–93 % of chronic HBV carriers (Caredda *et al.*, 1982; Camareno *et al.*, 1991). It has been proved that in chronic HBV infection the presence of HBsAg/IgM is closely related to the presence of HBeAg in serum (Musca *et al.*, 1984). This was confirmed also by our results. In Senegal complexes were detected in HBeAg positive cirrhosis of the liver and primary carcinoma of the liver in 75 % (Coursaget *et al.*, 1986). They demonstrated in the same paper that the proportion of HBsAg/IgM complexes in anti-HBe positive sera rose from 5 % in chronic hepatitis to 29 % in cirrhosis and 42 % in hepatocellular carcinoma.

During concurrent infection with HBV and the virus of delta hepatitis (HDV) the synthesis of HBsAg is reduced and therefore a relative decline of titers of HBsAg/IgM complexes occurs (Craxi *et al.*, 1985). This fact could not influence our results because the incidence of HDV infection in chronic HBsAg carriers in the Czech Republic is very low – 0.3 % (Stránský *et al.*, 1989).

A significant correlation was also found between HBsAg/IgM complexes and HBV DNA polymerase activity ($p < 0.001$) and the receptor level for polymerized human serum albumin ($p < 0.001$). Patients with positive HBsAg/IgM

complexes had a significantly higher ALT activity than patients without complexes (Mora *et al.*, 1987). This finding was found also in our patients.

In acute HBV infection the circulating immunocomplexes are probably responsible for extrahepatic symptoms. In chronic infection the immune complexes are fixed on liver cells, as proved by immunohistochemical methods and thus their participation in hepatocyte damage is not probable but it cannot be ruled out completely (Manca *et al.*, 1984).

Our results confirm Musca's findings (1984) who found HBsAg/IgM complexes in 93 % of HBeAg positive chronic carriers. HBsAg/IgM complexes play therefore an important diagnostic and prognostic role not only in acute but also in chronic HBV infection.

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