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DISAPPEARANCE OF HEPATITIS B SURFACE ANTIGEN IN CHRONIC TYPE B HEPATITIS AFTER CLINICAL AND LABORATORIAL RELAPSE PRODUCED BY ABRUPT WITHDRAWAL OF IMMUNOSSUPPRESSIVE DRUGS

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SUMMARY

A male patient with chronic active type B hepatitis was submitted to an immunossuppressive treatment with prednisolone and azathioprine. The appearance of gastric bleeding due to acute erosive lesions required and abrupt withdrawal of these drugs. A striking rebound phenomenon was observed, with a severe deterioration of the patient. After improvement of the symptoms and biochemical changes, hepatitis B surface antigen and hepatitis B e antigen were no longer detected. Anti-HBs appeared ten months after last relapse.

INTRODUCTION

The use of corticosteroid therapy in patients with chronic type B hepatitis remains an area of active controversy [2]. Corticosteroids associated or not to azathioprine were occasionally used by some Authors [1,5,20,24] while others pointed to a deleterious effect of prednisone in a prospective, controlled study [8]. It is a well known fact that corticosteroids are less beneficial in chronic type B hepatitis than in the "autoimmune" form [15,16]. Furthermore, some Authors have observed some potentiating effects of immunossuppressive agents on the viral replication [12,14,19].

In a recent paper, MÜLLER et al. [11] suggested that rapid withdrawal of immunossuppressive therapy in some patients with chronic type B hepatitis and hepatitis B e antigen (HBeAg) may initiate a host response resulting in the elimination of HBeAg and improvement of clinical and biochemical abnormalities. Similar facts were observed by SCULLARD et al. [19] who showed that DNA polymerase (DNA-P) activity may become undetectable in some patients with chronic type B hepatitis after withdrawal of immunossuppressive therapy.

We report here the dramatic effects of rapid withdrawal of prednisone and azathioprine on clinical and biochemical parameters and B virus markers in a patient with chronic active type B hepatitis.

CASE REPORT

H.E.S., a 50-year old male, was first seen in December 1978 with a history of epigastric pain. He was well until two years before, when weakness and fatigue started. Past history revealed that he had suffered and unidentified hepatitis in 1966, apparently cured after 40 days of bed rest.

In December 1978, diagnostic investigation showed normal digestive tract by X-ray, normal blood count, alanine aminotransferase (ALT) 900 IU/L, aspartate aminotransferase (AST) 500 IU/L, gamma-glutamyl transferase (GGT) 27 IU/L. Total bilirubin was 1.1 mg/dl, prothrombin time 16 seconds with a control of

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12 seconds and a electrophoresis of serum protein showed albumin of 3.44 g/dl and gamma-globulin of 3.0 g/dl. Radio immunoassay (RIA) test for hepatitis B surface antigen (HBsAg) and anti-A virus, IgG type were positive; tests for detection of HBeAg were not performed at this time. No auto-antibodies were detected. In January 1979, laparoscopy was performed, showing the liver with irregular surface and small ill-defined nodules. Liver biopsy showed chronic active hepatitis of moderate severity.

After a temporary normalization of AST, this enzyme rose again to 440 IU/L. Prednisone, 40 mg daily, was then started, tapering to 10 mg/day over a period of 4 weeks. AST decreased to 40 IU/L but a second relapse occurred and 50 mg of azathioprine was associated to 15 mg of prednisolone daily (see Fig. 1). Clinical and biochemical responses were satisfactory up to April 1980, when the patient complained of nausea and dark stools. Gastroscopy then performed showed erosive hemorrhagic gastritis without esophageal varices. For this reason, prednisolone was interrupted and azathioprine reduced. In the next few days jaundice appeared for the first time and the patient presented weakness, ascitis and clinical signs of encephalopathy (somnolence, slurred speech and flapping). There was a progressive elevation of AST, serum total and conjugated bilirubin and gamma-globulin level, a decrease of albumin (Fig. 1) and prolongation of the prothrombin time (31 seconds, with a control of 12 seconds).

Two months afterwards the patient became assymptomatic with progressive normaliza tion of biochemical tests.

As far as hepatitis B virus markers were concerned, disappearance of HBsAg and HBeAg was observed. Anti HBs was detected for the first time 10 months after the last relapse (Fig. 1).

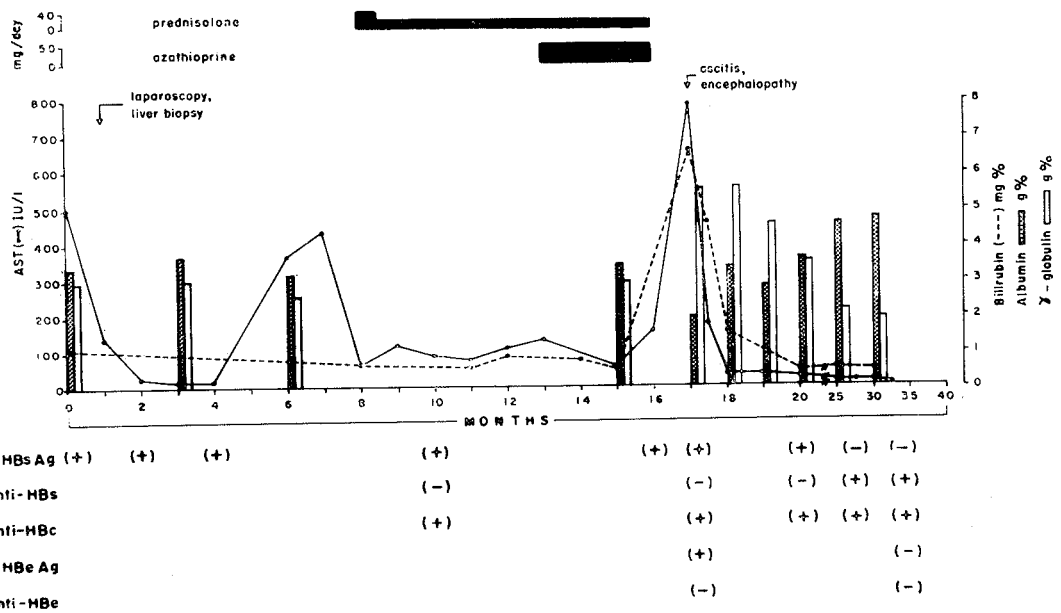

Fig. 1 — Clinical, biochemical and B virus marker changes after abrupt withdrawal of immunossuppressive treatment in a patient with chronic active hepatitis.

DISCUSSION

Although a new infection with delta agent cannot be excluded as a cause of the apparent deterioration, our case report suggests that severe complications can appear after abrupt withdrawal of an immunossuppressive treatment. This rebound phenomenon is a well-known fact[9]. However, the effects on B virus markers are poorly understood.

Some Authors[14,19] have demonstrated that corticosteroids alone or associated to azathio-

prine might be potentiators of viral replication. Thus, SCULLARD et al.[19] showed that the administration of prednisone to three patients with chronic active hepatitis B during 12 weeks led to increased DNA-P activity, moderated elevation in HBsAg titer and declined AST levels. After withdrawal of the corticosteroid, DNA-P activity fell in all of the 3 patients and became undetectable in 1 patient. HBsAg titers also fell but remained detectable in all 3 patients. AST activity rose substantially but then returned to the initial values.

In other 21 patients studied by the same Authors[19], DNA-P activity fell in all patients and became undetectable in 8 patients. HBsAg titers fell in 17 patients, but no patient became negative by radioimmunoassay. According to these Authors, a reasonable explanation for these occurrences after withdrawal of immunossuppressive drugs might be an improvement of the inefficient immune status of the host. It is also possible that there may be a rebound or "hyperimmune" condition after withdrawal[19]. In their patients, the schedule for withdrawal was slow, with no severe side effects observed.

HOOFNAGLE et al.[4] observed a reactivation of chronic hepatitis B virus infection in two patients under cancer chemotherapy. Both patients developed acute, icteric hepatitis within 3 months after starting cycled chemotherapy and both ultimately recovered, becoming seronegative for HBsAg. According to the same Authors, such reactivation is most likely due to an increase in hepatitis B virus synthesis followed by a rebound in host immune responses to hepatitis B virus infection when therapy is stopped. The absence of HBsAg after chemotherapy suggests that intentional reactivation of hepatitis could be one approach to the therapy of chronic hepatitis B virus infection[4].

However, GALBRAITH et al.[3] reported three HBsAg positive patients who developed fulminant hepatic failure after abrupt withdrawal of cytotoxic drug therapy. Also, evolution to subacute hepatic necrosis and probably to chronic active hepatitis was referred by WANDS[23].

According to MÜLLER et al.[11], a rapid withdrawal of immunossuppressive therapy in some patients with HBeAg positive chronic active hepatitis B may initiate a host response resulting in the elimination of HBeAg and improvement of clinical and biochemical abnormalities. Such possibility was also suggested by other Authors[6,24].

Our case report shows, however, that a sudden withdrawal of immunossuppressive drugs can be hazardous. Thus, a striking deterioration of the patient's liver function was observed, with the appearance of jaundice, ascites and pre-coma. As shown in Fig. 1, there was also a sharp increase of bilirubin and gamma-globulin levels. Gradually, however, the clinical condition and the biochemical data showed a progressive improvement. Presently, the patient is completely assymptomatic, the biochemical tests show normal values and, most important of all, the HBsAg became negative and the anti-HBs became positive. The disappearance of this marker has not been previously observed in our 53 patients with chronic active type B hepatitis (unpublished data), in 50 patients followed over a period of 2 — 7 years by REALDI et al.[13] and is only occasionally mentioned in the literature[10,14,21]. Despite some reports on a rapid clearance of HBsAg after the diagnosis of chronic active type B hepatitis[7], this fact is unusual[1,6].

As pointed out by VILLA et al.[22], until other cases of reactivation have been studied, it will not be clear whether the usual outcome is disappearance of the virus or re-establishment of the initial pattern of infection. Though we did not determine DNA-P activity the evolution of our patient suggests a type I response as described by SCULLARD et al.[17,18], which is caracterized by the loss of HBsAg, HBeAg and DNA-P.

Summing up, the therapeutic approach of corticosteroid therapy followed by its rapid withdrawal, though promising[6,11,24] should be considered with caution, at least in patients with chronic active hepatitis.

RESUMO

Desaparecimento do antígeno de superfície da hepatite B em hepatite crônica tipo B, após alterações clínicas e laboratoriais produzidas pela suspensão abrupta de drogas imunossupressoras.

Paciente com hepatite crônica ativa por vírus B foi submetido a tratamento imunossu-

pressor com prednisolona e azatioprina. Contudo, tal medicação foi bruscamente interrompida, em virtude de sangramento por gastrite erosiva hemorrágica. Observou-se, em seguida, grave deterioração do estado do paciente, com aparecimento de icterícia, ascite e sinais de encefalopatia hepática. Concomitantemente à melhora do quadro clínico, observou se desaparecimento do antígeno de superfície e do antígeno e da hepatite B. O anti-HBs surgiu dez meses após a recrudescência.

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