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Anti-HCV IgG avidity index in acute hepatitis C

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Abstract

Background: The diagnosis of acute hepatitis C (AHC) is based on seroconversion to positive anti-HCV, which is usually not clinically possible.
Objective: To determine if avidity of anti-HCV IgG can be used for the diagnosis of AHC infection.
Study design: We enrolled 40 consecutive patients with AHC, 16 drug addicts (IVDA) with exacerbation of chronic hepatitis C (IVDA e-CHC group), 21 non-IVDA with exacerbation of chronic hepatitis C (IVDA-free e-CHC group) and 40 with chronic hepatitis C (CHC group). HCV avidity index (HCV-AI) was determined by ELISA on sera pre-diluted 1:10 with 1M guanidine.
Results: On admission, HCV-AI values were significantly lower in the AHC group (mean ± S.D.: 0.50 ± 0.30) than in IVDA-free e-CHC group (0.97 ± 0.08, $p < 0.0001$), IVDA e-CHC group (0.90 ± 0.29, $p < 0.0001$) or CHC group (1.06 ± 0.20, $p < 0.0001$). An HCV-AI lower than 0.7 obtained within the 8th day of illness distinguished patients with AHC infection from the IVDA-free e-CHC cases. An increase in HCV-AI was observed in 24 (72.7%) of 33 in AHC group, in none of 13 in IVDA-free e-CHC group and in 3 (27.3%) of 11 in IVDA e-CHC group.
Conclusion: HCV-AI is useful in identifying AHC infection in patients observed within the 8th day from the onset of symptoms.

Keywords: Antibody avidity; Acute hepatitis C; HCV avidity index; Reactivation of chronic hepatitis C; Chronic hepatitis C; Anti-HCV

1. Introduction

Acute hepatitis C (AHC) infection is often asymptomatic and, therefore, frequently goes undiagnosed (Orland et al., 2001). Moreover, it is difficult to distinguish AHC infection from an exacerbation of chronic hepatitis C (e-CHC) on the basis of clinical, biochemical, virological and immunological data (Coppola et al., 2005; Rumi et al., 2002, 2005; Sagnelli et al., 2005; Sheen et al., 1996). An e-CHC, a clinical event that may occur in patients with chronic hepatitis C (CHC), is characterized by a substantial increase in the serum alanine-aminotransferase (ALT) value and in symptomatic cases by jaundice, asthenia and anorexia. The serum titers of IgM to the HCV core protein can distinguish these two clinical forms only if there is an increase or decrease in this antibody in three serial determinations (Sagnelli et al., 2005), which is a strong limitation to the use of this test in clinical practice. Thus, the demonstration of seroconversion to anti-HCV positivity remains the only easy method to identify AHC infection in patients who were known to be anti-HCV negative a few months before the illness.

The recent demonstration that patients with AHC infection show a high rate of sustained response after a short course of alpha-Interferon (IFN) treatment (Jaeckel et al., 2001; Kamal

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et al., 2004) underscores the need for early diagnosis of AHC infection.

In toxoplasmosis, cytomegalovirus, HIV, and HBV infections the measurement of IgG antibody avidity can be used to distinguish an acute from a chronic infection or from a reactivation of a chronic infection (Eggers et al., 2000; Jenum et al., 1997; Rodella et al., 2006; Suligoi et al., 2002). This method has also been proposed to distinguish acute hepatitis C from chronic hepatitis C (Kanno et al., 2002; Ward et al., 1994).

This paper describes a study on anti-HCV IgG avidity in 40 consecutive patients with AHC infection, 37 consecutive patients with e-CHC (16 with current intravenous drug addiction and 21 without), and 40 with HCV-RNA positive CHC infection. The clinical use of the anti-HCV avidity index (HCV-AI) in these patients is discussed.

2. Patients and methods

2.1. Patients

We investigated four groups of patients observed at our ward from January 2002 to June 2005:

(1) Forty consecutive patients with symptomatic AHC infection first observed 3–15 days after the onset of symptoms (AHC group); the diagnosis of AHC infection was made when the patients met the following criteria: (a) they had been anti-HCV negative with normal ALT values over the 4 months preceding the onset of symptoms; (b) they had detectable anti-HCV in serum and HCV-RNA in plasma and an ALT serum level of at least five times the upper normal value during the acute illness.

(2) Thirty-seven consecutive patients with symptomatic e-CHC first observed 4–13 days after the onset of symptoms; the diagnosis of e-CHC was made when: (a) the subjects had been anti-HCV/HCV-RNA positive for at least 1 year before the onset of symptoms (1–11 years in our cases), with normal or abnormal serum ALT value; (b) during the acute phase of the illness, anti-HCV and HCV-RNA were still detected with an abnormal increase in the ALT serum level of at least 5 times the mean of the values observed in the preceding 12 months; symptoms included jaundice, asthenia and anorexia. Since 16 patients in the e-CHC group were current Intravenous Drug Addicts (IVDA) at risk of acquiring a new HCV infection and, consequently, of developing a second episode of AHC indistinguishable from an e-CHC (Grebely et al., 2006; Herring et al., 2004), two groups of patients with e-CHC were formed: an "IVDA free e-CHC group" of 21 patients and an "IVDA e-CHC group" of 16 patients.

(3) Forty patients with asymptomatic HCV-RNA positive chronic hepatitis documented for 2–29 years (CHC group), observed in the same period and pair-matched with the 40 patients in the AHC group by age (±5 years), sex, and risk factors for the acquisition of parenteral infections.

The patients in the AHC, IVDA-free e-CHC and IVDA e-CHC groups were first observed at our Liver Unit during the symptomatic phase of the acute illness and then followed as outpatients. The patients in the CHC group were observed as outpatients.

Excluded from the study were patients with a history of alcohol intake, those treated in the last 6 months with drugs considered to be hepatotoxic, and those with serum positive for hepatitis B surface antigen (HBsAg) or anti-HIV antibody. Also excluded were AHC and e-CHC with antibody to hepatitis B core (HBc) antigen or IgM antibody to HBc, hepatitis D virus (HDV), hepatitis A virus (HAV), cytomegalovirus or anti Epstein Barr virus IgM at the time of first observation during the acute phase of the illness. The patients had never been treated with antiviral drugs active against hepatitis C infection (i.e. alfa-IFN, ribavirin).

Serum and plasma samples were obtained from each patient on enrolment and stored at −80 °C. During the acute phase of the illness serum and plasma samples were collected at 4–6 day intervals from 33 of the 40 patients with AHC infection; 13 of the 21 in the IVDA-free e-CHC group; and 11 of the 16 in the IVDA e-CHC group.

Of the 40 patients with AHC infection, 29 were followed as outpatients for 6–30 months and 7 for 3–5 months; 4 patients were lost to follow-up. Of the 21 patients in the IVDA free e-CHC group, 17 were followed as outpatients for at least 6 months and 4 for 3–5 months. Of the 16 patients in the IVDA e-CHC group, 9 were followed as outpatients for at least 6 months, 2 for 3–5 months, and 5 were lost to the follow up. Patients with AHC infection were considered to have recovered if they showed a remission of the clinical symptoms, normalization of the serum ALT value, and clearance of plasma HCV-RNA for at least 3 months. Persistence of plasma HCV-RNA for more than 6 months was considered progression to chronicity.

2.2. Routine methods

HAV, HBV and HDV serum markers were determined using a commercial immunoenzymatic assay (Abbott Laboratories, North Chicago, IL, USA, for HBsAg, anti-HBs and anti-HBc IgM, and DiaSorin, Saluggia, VC, Italy, for HBeAg, anti-HBe, anti-HDV IgG, and anti-HDV IgM). Anti-HCV antibody was sought using a third generation commercial immunoenzymatic assay (Ortho Diagnostic Systems, Neckargemund, Germany) and serum anti-HIV antibody by a commercial immunoenzymatic assay (Abbott Laboratories, North Chicago, IL, USA). Liver function tests were carried out according to routine methods. Plasma HCV-RNA was sought in all available plasma samples by a qualitative Reverse Transcriptase-Polymerase Chain Reac-