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Natural history of chronic viral hepatitis in southern Italy: epidemiological changes since the introduction of the anti-HCV test

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SUMMARY

We investigated whether there are differences between the natural history of B and C chronic hepatitis in a southern Italian population, and whether the chronic viral hepatitis population was modified by the introduction of the anti-HCV test in 1989. We examined clinical charts of 1120 patients consecutively admitted to our division from January 1979 to December 1998 with the histological diagnosis of chronic viral hepatitis (304 from 1979 to 1988; 816 from 1989 to 1998). We found significant differences only in age at diagnosis (higher in the second decade, $P = 0{\cdot}001$), and in aetiology (HBV decreased in the second decade, $P < 0{\cdot}0001$). We were able to follow up 449 patients for 2–20 years (311 with HCV and 138 with HBV infection), and found that chronic HCV evolved to cirrhosis more frequently than did chronic HBV; but in both types time to development of cirrhosis and the incidence of death were similar. Our data confirm that a higher onset age of HBV and of HCV is frequently observed in those subjects who have a faster disease progression.

INTRODUCTION

An understanding of the natural history of chronic viral hepatitis is important for making rational decisions about public health or therapeutic management of this disease. The introduction in 1989 of the assay for antibody to hepatitis C virus (anti-HCV) made it possible to identify a group of liver diseases which at that time were only suspected.

HCV infection occurs across all continents, and the worldwide prevalence of anti-HCV ranges from 1 to 2% [1]. In many countries hepatitis C infection is now the principal cause of hepatic disease requiring liver transplantation in adults [1]. Meanwhile, the occurrence of hepatitis B is clearly declining, probably because of behavioural changes among drug addicts and homosexuals in response to the AIDS epidemic [2]. Hepatitis B virus (HBV) vaccination, which has become obligatory in many industrialized countries, including Italy, may also have had an impact in lowering disease rates [2–4].

Most subjects infected with HCV and a significant proportion infected with HBV develop chronic hepatitis. The pathological progression of this disease is not completely understood because of the variability of the immune response by the host, the heterogeneity of the population studied, and the difficulty in establishing the time of initial viral infection once the disease has evolved to the chronic stage.

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Twenty per cent of patients with chronic HCV hepatitis develop cirrhosis within a decade or two [1]. There is a very wide range of susceptibility to development of cirrhosis, but it seems most frequent in males infected after the age of 50 years and in patients with a history of alcohol abuse [1]. Cirrhosis is reported to develop from hepatitis B infection within 3–7 years in 20% of cases, with a calculated annual incidence of 5–9% [4]. The presence of bridging hepatic necrosis, advanced age and persistence of HBV DNA in serum are associated with a poor prognosis [5].

In order to investigate whether there are differences between the natural history of chronic viral hepatitis B compared to C in a southern Italian population with this disease, and whether and how such a population was modified by the introduction in 1989 of the test for anti-HCV, we examined the clinical records of all cases of chronic viral hepatitis diagnosed in our unit from 1979 to 1998.

METHODS

We studied all cases (1120) of histologically diagnosed chronic viral hepatitis consecutively admitted to the Division of Hepato-gastroenterology at the Federico II University of Naples from January 1979 to December 1998. Of these patients, 92% were resident in Naples and its suburbs and the remaining 8% came from throughout southern Italy. All patients were examined prior to hospital admission by the same group of hepatologists, and histological evaluation was carried out by the same team of pathologists.

The aetiology of chronic hepatitis was identified on the basis of patient history, tests for HBsAg, for autoantibodies and, since 1989, for anti-HCV. Information regarding these patients' sex, age at liver biopsy and the therapy prescribed were recorded. In order to discover whether the chronic viral hepatitis population was modified by the introduction of the specific test for virus C hepatitis in 1989, we divided the patients according to the time of first admission to our department: either during the decade prior to the introduction of the anti-HCV test (1979–1989: 304 cases) or during the decade following this change (1989–1998: 816 cases).

To trace the natural history of chronic viral hepatitis, we excluded from the group of 1120 patients 392 patients who received antiviral therapy and 279 patients whose charts provided insufficient data. The patients thus selected and followed up for 2–20 years numbered 449.

During follow-up, patients underwent clinical and routine blood tests every 4 months, and an ultrasound procedure annually. When indications of cirrhosis were observed (noticeable hardening of the liver, appearance of thrombocytopaenia, reduced parameters of hepatic synthesis or ultrasound indications of spleen enlargement), liver biopsy was performed to detect the presence of cirrhosis. This generally occurred approximately 9 years after the histological diagnosis of chronic hepatitis.

Statistical analysis

Independent sample t test was used to compare group means for continuous variables. Bivariate correlations were calculated by computing Spearman's coefficient with significance levels. For frequency tables the χ^2 test was performed. For all analyses, probability values of 5% or less were taken to be statistically significant. Data were presented as mean $\pm$ S.D. The statistical analysis was performed using the SPSS software for Windows (release 11.0.1, 15 Nov. 2001; SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of the patients with histologically documented chronic viral hepatitis (1120 observations), divided into two decades according to the date of first admittance and grouped according to sex, age at diagnosis, aetiology, and therapy. No significant difference in sex distribution was found between the two groups but age at diagnosis was significantly higher ($P=0{\cdot}001$), and HBV infection significantly lower in the second decade ($P<0{\cdot}0001$). The latter finding is in agreement with international epidemiological data [2, 6]. There was a drastic decrease in the number of healthy carriers of HBsAg observed during the study period and not included in this study (Fig. 1).

In 20 years' observation of patients in our division, the annual incidence of admission to hospital for chronic viral hepatitis has not moderated (Fig. 2).

The number of cases of HCV chronic hepatitis, which could only be verified since 1989 when the specific assay became available, was statistically higher than that of non-A/non-B (NANB) hepatitis in the first decade ($P<0{\cdot}0001$).

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Table 1. *Chronic viral hepatitis patients: comparison between first and second decades*

	First decade (1979–1988)	Second decade (1989–1998)	*P*
Observations, *n*	304	816	
Gender M/F, *n* (%)	192/112 (63/37)	503/313 (62/38)	0·64[a]
Age (years) at diagnosis (mean ± S.D.)	42 ± 16	45 ± 13	0·001[b]
NANB chronic hepatitis, *n* (%)	141 (46)	16 (2)	<0·0001[a]
HCV chronic hepatitis, *n* (%)	0 (0)	517 (63)*	<0·0001[a]
HBsAg$^+$ chronic hepatitis, *n* (%)	163 (54)	285 (35)	<0·0001[a]
Immunotherapy, *n* (%)	148 (49)	76 (9)	<0·0001[a]
No therapy, *n* (%)	156 (51)	369 (45)	0·07[a]
IFN therapy, *n* (%)	0 (0)	292 (36)	<0·0001[a]

[a] By χ^2 test.
[b] By unpaired *t* test.
* *vs.* NANB chronic hepatitis in the first decade, $P<0{\cdot}0001$[b].

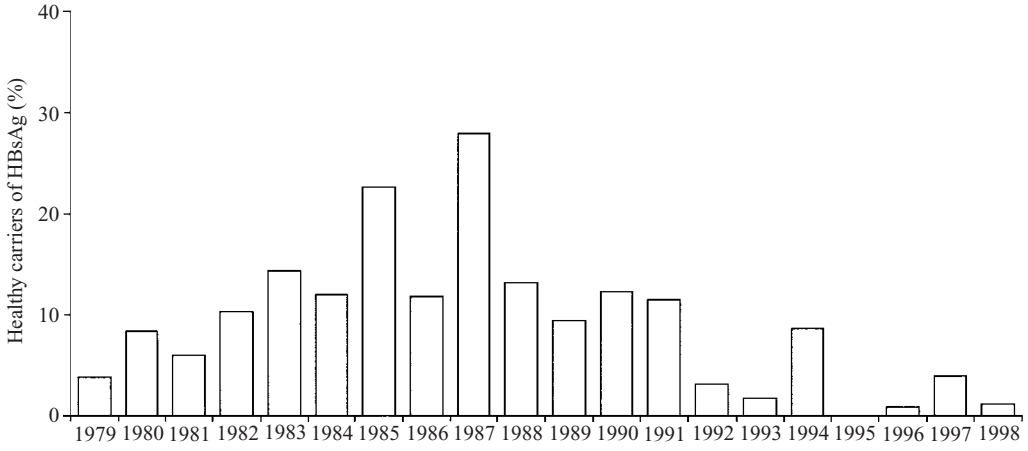

Fig. 1. Number of HBsAg carriers observed between 1979 and 1998.

The following analysis concerned 449 untreated patients followed up for 2–20 years, of whom 311 were positive for HCV and 138 for HBV. All cases diagnosed as NANB chronic hepatitis during the first decade of observation, when tested after 1989, turned out to be anti-HCV-positive (82 observations).

Liver cirrhosis confirmed by biopsy occurred in 27% of patients (84 cases) with HCV chronic hepatitis after a mean interval of 83 ± 24 months (range 36–156 months), and in 10% of patients (14 cases) with HBV chronic hepatitis after a mean interval of 86 ± 21 months (range 12–168 months). We observed a significant difference in frequency of progression between the two groups ($P<0{\cdot}0001$), but not in the time interval from diagnosis of hepatitis to that of cirrhosis ($P=0{\cdot}21$).

Death occurred in 4% of HCV patients (12 cases) at a mean interval of 130 ± 25 months (range 44–170) after diagnosis and in 7% of the HBV patients (10 cases) at a mean interval of 127 ± 27 months (range 18–175) after diagnosis, without a statistically significant difference between the two groups ($P=0{\cdot}13$ and 0·23, respectively).

Our data confirm a direct correlation between age of onset of both chronic HBV and HCV hepatitis and severity of prognosis (onset age and progression to cirrhosis, $r=0{\cdot}458$, $P<0{\cdot}0001$; onset age and death, $r=0{\cdot}251$, $P<0{\cdot}0001$).

As to the causes of the infection, we established five principal categories: transfusions, medical treatment, household contact, drug abuse, and unknown. We found that HCV infection resulted from transfusions

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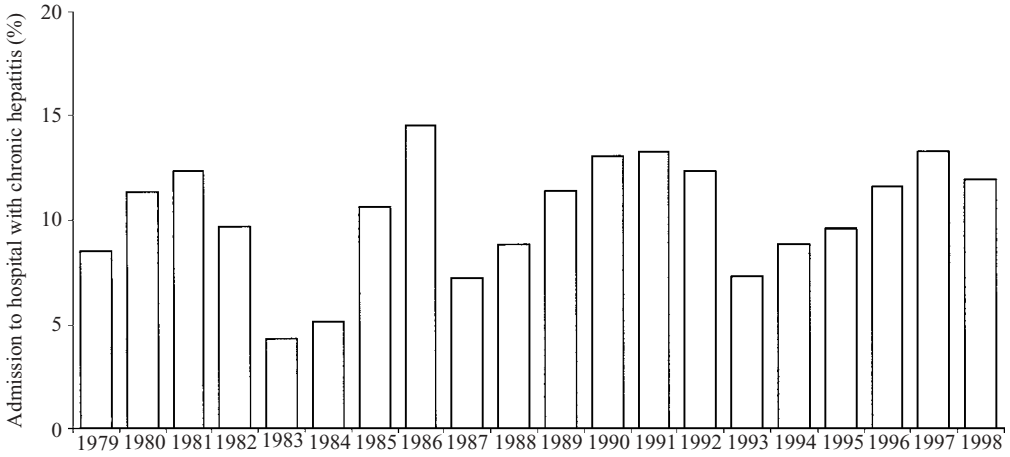

Fig. 2. Number of patients with chronic hepatitis observed between 1979 and 1998.

in 15·2% of cases, medical treatment in 34·6%, household contact in 10·7%, drug addiction in 8·0% and unknown in 31·5%. HBV infection resulted from transfusions in 2·0% of cases, medical treatment in 33·3%, household contact in 29·7%, drug addiction in 6·0%, and unknown in 29·0%.

The prevalence of viral infection in stable sexual partners of patients was significantly higher for HBV ($n=30$, 22%) than for HCV ($n=31$, 10%), with $P=0{\cdot}0003$.

The genotype of HCV in this study sample was 1b in 87% and 2a/c in 13%; there was no difference in origin of infection between the two genotypes.

DISCUSSION

In 20 years' observation, the annual incidence of admissions to our division has not changed, while the incidence of HBV carriage has gradually decreased (Fig. 1) due to the precautions generally observed since 1970 when HBsAg was identified. Among these were the search for HBV in donated blood, the adoption of disposable syringes, HBV vaccination and better compliance with procedures for sterilization of surgical instruments for minor operations, e.g. dental care [2, 3, 6, 7]. The higher incidence of HCV chronic hepatitis in the second decade with respect to that of NANB chronic hepatitis in the first decade does not represent a real increase in the prevalence of this viral infection. These data would be difficult to explain, given the lower infectivity of HCV than that of HBV and the fact that the viruses are transmitted in a similar way [6–9]. Although statistically significant, we suggest that this increase merely reflects the recent attention given to even very slight increases of alanine transferase activity, typical of this disease, which before the anti-HCV test, had been diagnosed as 'non-specific', and non-chronic hepatitis. In fact, the initial development of hepatitis C, more often than that of hepatitis B, is usually asymptomatic and the levels of alanine transferase activity are often in the normal range or only slightly increased. The prevalence of chronic hepatitis was higher in males in the whole period of observation (63 *vs.* 37% in females) with no significant difference between the two decades (Table 1).

The mean age at diagnosis was significantly higher in the second decade reflecting the reduced incidence and prevalence of hepatitis B in the general population in recent years. In fact, HBV chronic hepatitis is usually diagnosed at an earlier age (29 ± 43 *vs.* 44 ± 58 years for HCV) because it triggers higher levels of transaminases and is routinely tested for due to its frequent spread in families.

The frequency of progression to cirrhosis in our population, for both B and C hepatitis, agrees with previous reports [1, 2, 6, 10]. Liver disease evolved to cirrhosis more frequently in the HCV patients than in the HBV patients (27 *vs.* 10%, respectively), but within the same interval after diagnosis.

No significant difference was found either in occurrence of death (7 *vs.* 4%), nor in time elapsed between diagnosis of chronic hepatitis and occurrence of death between patients with hepatitis B and C. The most frequent cause of death in both groups was haemorrhage.

The aetiology of acute viral hepatitis in Italy is monitored by the Sistema Epidemiologico Integrato dell'Epatite Virale Acuta (SEIEVA) system [11]. Their data on acute hepatitis C for the year 2000 reveal

a completely different pattern of risk factors with respect to those of our chronic patients: the most frequent cause now is drug addiction (33%), while transfusions now cause less than 1%. The number of cases without an associated risk factor still remains high (35%). Even though these acute data refer to Italy as a whole, and our data refer only to Naples and its province, the values of risk factors 'unknown' and 'household contact' are virtually identical in the two groups. The widely differing values for the risk factors 'blood transfusion' and 'drug addiction' are obviously due to changes over the past 20 years in worldwide phenomena. This suggests that the two groups can be considered valid for comparative purposes. Moreover, for risk factors in acute virus B hepatitis we observed a similar pattern with respect to those of our chronic patients. It is interesting that the risk factors 'household contact' (28 *vs.* 29·7%) and 'medical exposure' (42 *vs.* 33·3%) remain very high.

Although the single HCV genotype 1b was very prevalent in our population the natural history of hepatitis is not greatly different from that described in study populations from other countries; this finding suggests that the genotype may not influence the natural history of the disease.

In conclusion, in the population studied, HCV chronic hepatitis evolved to cirrhosis more frequently than did HBV, even though the time to development was similar. Prevalence of HBV infection was markedly lower in the second decade of our study. The most frequent sources of HBV infection were household and sexual contacts.

The causes of HCV infection have clearly changed in frequency over the last years but in a high percentage of cases the cause remains unknown. In our HBV- and HCV-infected population, development to cirrhosis appeared to be more frequent in patients with a higher age at diagnosis. This finding could be due to an impaired immune system, common in older people, leading to persistent viral replication and continuous liver damage.

The data concerning our chronic hepatitis population (age at diagnosis, predominating sex, percentage of development to cirrhosis and duration of the illness) are in agreement with medical literature relating to populations of the United States, northern Europe and northern Italy, which all differ from our population for HCV genotype and living conditions. This observation, in agreement with histological findings by Poynard [12], strengthens the view that the development of chronic viral hepatitis is not influenced by viral genotype or by the cause of infection, but rather by the immune response of the host, associated pathological conditions and risk factors related to life-style.

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