Digestive and Liver Disease 48 (2016) 1066–1071

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Epidemiological and clinical scenario of chronic liver diseases in Italy: Data from a multicenter nationwide survey

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ARTICLE INFO

Article history:
Received 13 February 2016
Accepted 16 May 2016
Available online 26 May 2016

Keywords:
Chronic hepatitis
Chronic liver diseases
HCC
Liver cirrhosis

ABSTRACT

Background: The last Italian prevalence survey on chronic liver diseases (CLD) was performed in 2001. The present study evaluated the changes occurring over thirteen years.
Methods: We enrolled 2,557 CLD consecutive patients in 16 Italian liver units in 2014.
Results: HBV etiology accounted for 513 (20.2%) cases, alone in 439 and associated with HCV and/or alcohol abuse in 74. Of these 513, 11.9% were anti-HDV-positive and 7.2% HBeAg-positive. HCV alone was responsible for 50.3% of CLD and with alcohol abuse for 5.9%. HCV RNA was detected in 64.0% of the anti-HCV-positive patients tested. HCV genotyping, performed for 899 patients, showed genotype-1a, 1b, 2, 3, 4 and 5 respectively in 16.5%, 45.5%, 15.4%, 8.2%, 15.1% and 0.2%. Alcohol abuse alone was responsible for 6.4% of cases and NAFLD/NASH for 6.3%. Liver cirrhosis ($p < 0.001$) and HCC ($p < 0.001$) were more frequent in alcoholic than viral etiologies. HCV and alcohol etiologies were more frequent in 2001 than 2014 (from 69.9% to 59.9% and from 23.0% to 12.3%, respectively). HBV showed a similar impact. In all etiologies, the 2001 CLD cases were 10 years younger and with a significantly lower rate of cirrhosis than the 2014 cases.
Conclusion: The changes in HCV, HBV and alcohol etiologies may help apply more appropriate healthcare strategies.

1. Introduction

An Italian multicenter retrospective study performed on 1,154 patients with chronic liver diseases (CLD) enrolled from 1976 to 1981 showed that 60% of the cases were HBsAg-positive and the remaining 40% HBsAg-negative. In the absence of a specific test for HCV etiology, the HBsAg-negative cases were attributed to a Non-A Non-B agent [1] and other etiologies remained unexplored. HBV etiology was observed in 31.3% of 5,461 cases with CLD studied from 1980 to 1989 [2] in another Italian multicenter prevalence survey in which 46.4% of the cases were attributed to a Non-A Non-B agent, 3% to an autoimmune etiology, 10.8% to alcohol abuse and 2.9% to other less frequent etiologies. An HBV/HDV multiple infection was diagnosed in 5.5% of the HBsAg-positive cases.

A further impressive decline in HBV etiology was observed in a prospective multicenter investigation on 9,997 Italian patients with chronic liver disease studied in 79 liver units in 2001 [3]. In this study, 10% ($n = 1,000$) of the cases were due to HBV infection alone, 1.4% ($n = 140$) were HBV/alcohol-related, 1.4% ($n = 141$)

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http://dx.doi.org/10.1016/j.dld.2016.05.014
1590-8658/

HBV/HCV-related and 0.6% ($n = 63$) HBV/HCV/alcohol-related. In addition, 56.3% ($n = 5,632$) of the cases were due to HCV infection alone, 11.6% ($n = 1,163$) were HCV/alcohol-related, 9.4% ($n = 935$) alcohol-related, 0.8% ($n = 76$) autoimmune, 0.5% ($n = 25$) PBC, 4.4% ($n = 444$) NALFD and the remaining 3.6% were attributed to other infrequent etiologies. An HBV/HDV multiple infection was detected in 9.7% of the HBsAg-positive cases. These prevalences remained substantially unchanged when only the 6,210 patients with chronic hepatitis were evaluated [4]. These data indicate a decrease in the rate of HBV-related cases from 1976 to 2001 and a corresponding increase in the rate of the HCV-related cases.

The lack of information on these trends after 2001 induced us to conduct a new prospective multicenter prevalence survey on the etiology of CLD in Italy.

2. Materials and methods

2.1. Study population and methods

The present study, named the EPACRON study, recruited 2,557 patients with CLD from January to December 2014. The enrolling criteria were age over 18 years and patients admitted for either altered hepatic biochemistry or presence of etiologic markers of liver diseases or referring symptoms consistent with CLD. Both in- and outpatients were consecutively admitted to one of 16 cooperating Liver Units located in different Italian regions. Of the 16 participating Liver Units, 7 were clinical centers of Departments of Infectious Diseases, 5 of Departments of Gastroenterology and 4 of Departments of Internal Medicine. Nearly two-thirds of patients were recruited in Liver Units of Departments of Gastroenterology or Internal Medicine and nearly one third in Liver Units of Departments of Infectious Diseases. Several of these centers have cooperated for a decade in numerous clinical investigations applying the same clinical approach and similar analytical methods [5–7].

The collection of personal data was made in full compliance with the Italian law on personal data protection, and each patient gave his/her informed consent to participate. All procedures applied in the study were in accordance with the international guidelines, with the standards of human experimentation of the local Ethics Committees and with the Helsinki Declaration of 1975, revised in 1983. At the time of the first observation, each patient signed their informed consent for the collection of personal data, as designated by the Ethics Committee of the coordinating center. Patients who agreed to undergo liver biopsy signed an appropriate informed consent before biopsy was performed. All patients were included only once, even if seen several times during the observation period. For each patient a pre-coded questionnaire containing demographic, epidemiological and clinical data was filled out. No patient refused to participate in the study.

The presence of serum HBsAg identified an HBV etiology, and the detection of anti-HCV an HCV etiology. Autoimmune chronic hepatitis and primary biliary cholangitis were diagnosed according to standardized international criteria [8–10]. The diagnosis of hereditary hemochromatosis was made on the basis of abnormal ferritin serum values and transferrin saturation serum values, genetic markers, or liver histology [8,11]. Wilson's disease was a rare diagnosis, made on the basis of accepted criteria [8,12]. The presence of a metabolic syndrome was established based on accepted criteria [8].

Abnormal serum alanine aminotransferase (ALT) values and a histological and/or ultrasound pattern of hepatic steatosis, in the absence of other known causes of chronic liver disease, were considered related to non-alcoholic fatty liver disease [13]. An alcohol intake $\geq$40 g/day for males and $\geq$30 g/day for females for at least 5 years was considered an etiologic factor of liver disease. A cryptogenic chronic liver disease was diagnosed in the absence of any viral, autoimmune or metabolic etiology. Chronic hepatitis was diagnosed on the basis of liver histology, when available, or on the persistence (>6 months) of abnormal ALT in the absence of clinical, biochemical, and ultrasound markers of liver cirrhosis [8,14]. Liver cirrhosis was diagnosed by liver biopsy (LB) or on the presence of characteristic clinical, biochemical, and ultrasound signs [8,14]. The diagnosis of hepatocellular carcinoma (HCC) was based on histological and/or imaging findings and alfa-1-fetoprotein serum levels, according to accepted criteria [8,15]. Percutaneous LB was performed, if requested by the physician in care for diagnostic purposes, under US guidance using a disposable modified Menghini needle. In each liver unit a skilled pathologist unaware of the clinical and laboratory data evaluated liver histology. In particular, liver necroinflammation and fibrosis were assessed by the Ishak [16] or Metavir scoring system [17], and standardized criteria were used to convert the Ishak score to a Metavir score [18]. Transient elastometry was performed by Fibroscan [19,20]. Serum HBsAg and antibody to HCV, HDV and HIV were sought using commercial immunoenzymatic assays. Plasma HBV DNA was determined by real-time polymerase chain reaction (PCR) [21]; by this method, the detection limit in plasma samples is estimated at around 40 IU/mL. HCV RNA was detected and quantified by a real-time PCR in a Light cycler 1.5; by this method, the detection limit in plasma samples is estimated at around 40 IU/mL. HCV genotyping was performed using a commercial Line-Probe assay.

Routine tests were applied to seek the etiologic markers of autoimmune hepatitis, PBC, iron and copper overload and liver functions.

2.2. Statistical analysis

The data were collected in a pre-established electronic CRF database (web-based data collection, e-CRF provided by Air-Tel®, Airon Telematica, Milan, Italy). Differences in the distribution of the characteristics of the subjects in the different groups were evaluated applying the analysis of variance and the Chi-square analysis for continuous and categorical variables, respectively. A p value less than 0.05 was considered statistically significant. All p values were two-tailed.

3. Results

At the end of the recruitment period, 2,557 patients with chronic liver diseases had been consecutively enrolled. Males predominated ($n = 1,512/59.1\%$) and the majority of patients were of Italian/Caucasian origin ($n = 2,420/94.7\%$). Less than one-third of the cases had a high school diploma or degree. Incidental finding on screening accounted for 80.7% ($n = 2,064$) of the patients enrolled and 86.0% ($n = 2,200$) were observed as outpatients (Table 1). Current alcohol abuse was stated by 12.0% ($n = 307$) of the patients enrolled in the present study, past alcohol abuse by 18% ($n = 460$), whereas 54% ($n = 1,381$) were abstainers or "social drinkers"; no or doubtful information was given by the remaining 16% ($n = 409$) (Table 1). Type-1 diabetes was present in 4.5% ($n = 116$) of patients and type-2 diabetes in 9.6% ($n = 245$). Compared with the 2,200 outpatients, the 357 inpatients were older (62.4 ± 12.9 vs. 58.3 ± 14.0, $p \leq 0.001$), prevalently males ($n = 228/63.9\%$ vs. $n = 1,284/58.4\%$, $p = 0.05$) and more frequently showed decompensated cirrhosis or HCC ($n = 225/45.2\%$ vs. $n = 609/10.7\%$, $p \leq 0.001$) (Table 2). Compared with inpatients, outpatients more frequently showed HBV ($n = 396/18\%$ vs. $n = 43/12\%$) and HCV etiology ($n = 1,119/50.9\%$ vs. $n = 167/46.8\%$) and less frequently alcoholic ($n = 130/5.9\%$ vs. $n = 33/9.2\%$) etiology and virus $\pm$ alcohol (6.6% of 146 vs. 13.4% of