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Background The last Italian prevalence survey on chronic hepatitis (CH) conducted in 2001 showed that the hepatitis C virus (HCV) was the main agent associated with CH.

Aim The aim of this study was to evaluate epidemiological changes in CH occurring after 13 years. Patients and methods Enrollment of 1392 CH consecutive patients referred to 16 Italian liver units in 2014 scattered all over the country (four in the North, four in the Center, four in the South, and four in the Islands) was performed.

Results The mean age of the patients was 58.3 years, with a sex ratio (male/female) of 1.5. HCV infection (also with other etiologies) continues to be the most prevalent etiology (58.1%). However, this prevalence was lower ($P<0.01$) than the corresponding figure (76.5%) for 2001. The proportion of hepatitis B virus-related cases almost doubled over time from 12.2% in 2001 to 22.5% in 2014 ($P <0.01$), most probably biased because of the distribution of entecavir and tenofovir free of charge at outpatient hospital clinics after 2001. Patients reporting risky alcohol intake (also with other etiologies) accounted for 12.4% of cases, a figure lower than that reported in 2001: 19.2% ($P <0.01$). The proportion of nonalcoholic fatty liver disease cases nearly doubled over time (3.6% in 2001 and 6.2% in 2014; $P< 0.05$), reflecting the greater attention over time devoted to this syndrome.

Conclusion The decreasing role of HCV infection as an etiologic factor of CH in Italy is good news considering the high cost of the directly acting antiviral agents for HCV eradication. Metabolic factors warrant greater attention in the near future.

Introduction

There is a long tradition of multicenter collaborative studies on the etiology of chronic liver diseases (CLDs) in Italy and a changing pattern of the etiologic agents has been observed over time. For chronic hepatitis (CH), most cases were associated with hepatitis B surface antigen (HBsAg) positivity during the 1970s [1,2], whereas during the 1980s, a downtrend in HBsAg positive cases was observed, associated with an increase in the proportion of non-A/non-B cases, most of which should be considered hepatitis C virus (HCV) related [3]. The last survey, conducted in 2001, showed that the main agent associated with CH was HCV, found alone in 62.6% of patients and associated with other etiologies in 76.5% of cases [4].

As no data were available after 2001, we conducted a further national survey in 2014 to assess the status of CH in Italy according to the etiologic factors and other epidemiological characteristics.

Patients and methods

Patients

The study population consisted of individuals with CLD aged older than 18 years with altered hepatic biochemistry or presence of etiologic markers of liver diseases or reporting symptoms consistent with CLD consecutively referred from January to December 2014, as inpatients or outpatients, for liver disease evaluation to one of the 16 liver units participating in this investigation. The participating units were situated all over the country (four in the North, four in the Center, four in the South, and four in the Islands). The hospitals were chosen on a voluntary basis. They were both district general and university hospitals; several of these centers had also participated in the 2001 survey. Access to clinical centers was comparable between the two surveys. The same methods as in the 2001 survey were used. The data were prospectively collected. CH was diagnosed on the basis of liver histology when available or on the persistence for more than 6 months of abnormal serum alanine aminotransferase levels in the absence of clinical, biochemical, and ultrasound markers of liver cirrhosis [5].

The presence of serum HBsAg identified an etiology of hepatitis B virus (HBV). Positivity of serum anti-HCV and HCV-RNA by PCR identified an HCV etiology. Autoimmune CH and primary biliary cholangitis were diagnosed according to standardized international criteria [6,7]. 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]. Wilson's disease was a rare diagnosis made according to established criteria [9].

Abnormal serum alanine aminotransferase values and a histological and/or ultrasound pattern of hepatic steatosis, in the absence of other known causes of CLD, were considered to be related to nonalcoholic fatty liver disease (NAFLD) [10]. The amount of alcohol intake was determined using a standard questionnaire containing information on the daily intake of various alcoholic beverages and the lifetime duration of alcohol consumption. A patient was considered to have alcohol-related CH if he/ she had a history of alcohol intake of more than 40 g/day for men and 30 g/day for women for at least 5 years, without any other pathogenic factor [11,12]. The etiology of CLD was considered undefined in the absence of any viral, autoimmune, or evident metabolic agent. 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, established in full agreement with the rules of the ethics committee of the coordinating center (A.O.U.P. of the University of Palermo, Italy). Patients who agreed to undergo liver biopsy (LB) signed appropriate informed consent before this procedure was performed. All patients were included in the study only once, that is, at their first observation during the study period. For each patient, a precoded questionnaire containing the demographic, epidemiological, and clinical data was completed.

Methods

Percutaneous LB was performed if requested by the treating physician for diagnostic purposes, under ultrasound guidance, using a disposable modified Menghini needle. At each liver unit, a skilled pathologist unaware of the clinical and laboratory data evaluated the liver histology. In particular, liver necroinflammation and fibrosis were assessed by the Ishak [13] or Metavir scoring system [14] and standardized criteria were used to convert the Ishak score into a Metavir score [15]. Serum HBsAg and antibodies to HCV, HDV, and HIV were determined using commercial immunoenzymatic assays. Routine tests were applied to determine the etiologic markers of autoimmune hepatitis, primary biliary cholangitis, iron, and copper overload, and liver functions.

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 patients in the different groups were evaluated by analysis of variance and the $\chi 2$-analysis for continuous and categorical variables, respectively. A P value less than 0.05 was considered to be significant. All P values were two tailed.

Results

Out of 2557 patients observed, 1392 (54.4%) had CH. LB was performed for 526 (37.8%) cases. The demographic characteristics of the CH patients are shown in Table 1. The mean age was 58.3 years (range: 18–90 years), with a male preponderance (59.6%). The proportion of Italian natives was 94.5%. The impact of the etiologic agents of CH observed in the present study is shown in Table 2 in comparison with the data of the 2001 survey [4]. HCV infection (also with other etiologies) continues to be the most prevalent (58.1%), but compared with the corresponding figure for 2001 (76.5%), the decrease is substantial and statistically significant ($P<0.01$). A significant

decrease was also observed in the proportion of cases reporting risky alcohol intake: from 19.2% in 2001 to 12.4% in 2014 (P<0.01). In contrast, the proportion of HBV-related cases almost doubled over time: from 12.2% in 2001 to 22.5% in 2014 (P<0.01). It is noteworthy that the proportion of hepatitis B e antigen-positive cases among the HBsAg-positive decreased from 16.6% in 2001 to 9.3% (P<0.05) in 2014. Finally, the proportion of cases defined as NAFLD nearly doubled over time (3.6% in 2001 and 6.2%in 2014; P<0.05). The temporal impact of the main etiologic agents in the last four decades shows that HCV-related cases (also with other etiologies) peaked in 2001 (76.5%) and decreased significantly to 58.1% by 2014 (P<0.01), but HCV is still the main etiologic agent (Table 3). A significant decrease was also observed in the proportion of cases reporting risky alcohol intake: from 19.2% in 2001 to 12.4% (P< 0.01) in 2014. Instead, after a continuous decrease from 44.0% in 1980 to 12.2% in 2001, HBV-related cases surprisingly increased to 22.5% in 2014 (Table 3). The decrease in hepatitis B e antigen positivity among HBsAg positive patients is also noteworthy (from 16.6% in 2001 to 9.3% in 2014). The proportion of cases defined as NAFLD almost doubled over time (3.6% in 2001 and 6.2% in 2014; P<0.05). The demographics of the CH cases observed in Italy in 2014 were analyzed according to the main etiologic factors (Table 4). Patients with risky alcohol intake were older than those in other etiologic groups and HBV-related cases showed the highest male/female ratio; these differences, however, were not statistically significant. Compared with the patients from central Italy and southern Italy + the islands, those from northern Italy less frequently showed HBV etiology (P<0.0001), more frequently had alcoholic liver disease (P=0.004) and NAFLD (P=0.003), and a similar frequency of HCV etiology (Table 4).

Discussion

As several liver units participating in the current survey also took part in the 2001 investigation, the results of the two studies can be considered comparable in terms of methodology adopted, geographical area, and ease of access to a clinical center. In addition, the geographical distribution

of the liver units throughout the country supports generalization of the findings to the whole of Italy. HCV infection continues to be the most common etiologic factor associated with CH in Italy. However, compared with the study carried out in 2001 [4], there has been a marked decrease in the proportion of HCV cases from 76.5 to 58.1% ($P<0.01$). We predicted this decline in our previous paper [4] on the basis of the much higher rates of HCV etiology in prevalent than in incident cases, showing a decrease in the proportion of newly diagnosed HCV-related cases. This decline was also observed in a recent population-based survey in southern Italy, which showed that the rate of anti-HCV positivity in the general population was 12.6% in 1996 but 5.7% in 2010 [16]. The downtrend of HCV infection in Italy reflects a cohort effect (i.e. decreased exposure to the virus along generations). In fact, population-based surveys have shown that HCV infection in Italy is mostly confined to the oldest age groups [16–19] as a consequence of past iatrogenic transmission not yet operating [18,20]. The impact of the effective directly acting antiviral (DAA) combination therapies for HCV infection on this downtrend can be excluded as this therapy was introduced in Italy only in 2014 and was limited to patients with a more severe liver disease (i.e. liver cirrhosis). In contrast, the increased prevalence of HBV-related cases from 2001 to 2014 probably reflects the availability, from 2001, of highly effective, easy to administer drugs (adefovir plus lamivudine, entecavir, or tenofovir) distributed free of charge at outpatient hospital clinics.

The proportion of patients with CH reporting risky alcohol intake alone is low and stable over time, but has decreased in anti-HCV-positive patients (from 12.6 to 5.0%) because of the general decline in the number of patients harboring HCV infection. Another tenable explanation, however, is that HCVpositive patients receive strong advice to avoid alcohol intake. NAFLD is emerging as one of the most important causes of CLD in industrialized countries, where unhealthy and sedentary lifestyles are leading to an increase in metabolic disorders [21].

The increase observed in the proportion of CH NAFLD cases, almost double from 2001 to 2014, may reflect increasing attention to the diagnosis of NAFLD over time. However, the prevalence of this etiology in the hospital setting is most probably underestimated because patients are often

asymptomatic and tend not to seek medical care until symptoms emerge. In accordance with this, a study carried out on the general population of a town in southern Italy showed that NAFLD was the most probable cause of as many as 24% of cases with altered biochemical serum liver tests [17].
In the present survey, potential referral biases should be considered. Factors affecting the prevalences observed may be poor awareness of a specific disease (the case of NAFLD), availability of new antiviral drugs (the case of HBV), and the tendency of patients with a given etiologic factor to seek medical care only once symptoms have appeared (the case of risky alcohol intake). Another bias is that patients included are only those referred to liver units. It is unlikely to accurately estimate the burden of each single etiology of CH in Italy as only patients who have undergone serological testing for hepatic biochemistry and/or etiologic markers of liver diseases are referred to a liver unit. The data of the present study, although providing interesting information on patients referred to one of the 16 participating liver units and reflecting general prevalence patterns, may hardly be considered representative of the overall prevalence of the etiological agents of CH in Italy. This updated survey highlights the decreasing role of HCV infection as an etiology of CH in Italy, which is good news considering the high cost of the DAAs for HCV eradication. HCV, however, remains the most prominent etiology responsible for CH in Italy, and only unlimited distribution free of charge of DAA therapy will bring about a further marked decrease in the HCV epidemiology [22]. The data from the present study also suggest that metabolic factors warrant greater attention, perhaps through media campaigns directed at the general population and more active sensitization of family doctors to refer patients with metabolic diseases for further investigation.

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Conflicts of interest

There are no conflicts of interest.

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