Incidence of adult form of autoimmune hepatitis in Valencia (Spain)

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Abstract

Background and study aims : **There is little information on the incidence of autoimmune hepatitis (AIH) because on many occasions the disease can progress asymptomatically, different diagnostic criteria have been proposed during the last 20 years, and many epidemiological studies are based on retrospective clinical series. The aim of this study was to determine the incidence of AIH in the province of Valencia, Spain, during the year 2003.**

Patients and Methods : **The Services of Gastroenterology of eight acute-care reference hospitals in the province of Valencia, Spain, covering 1,774,736 inhabitants over 14 years of age, participated in a prospective study. All newly diagnosed patients with AIH between January 1, 2003 and December 31, 2003 were eligible. The diagnosis was based on criteria of the International Autoimmune Hepatitis Group revised in 1999.**

Results : **There were 19 new cases of AIH, 18 females and 1 male [mean (SD) age of 54.3 (11.2) years, range 23-73]. Incidence peaked in the 45-54 year age group. Eighteen cases were classified as AIH type 1 and one case as AIH type 2. The incidence rate of AIH for the year 2003 in people older than 14 years of age was 1.07 new cases per 100,000 inhabitants, with 1.96 cases per 100,000 inhabitants in females and 0.12 cases per 100,000 inhabitants in males.**

Conclusions : **The 2003 annual incidence of AIH in Valencia, Spain, was similar to that reported in other European countries. AIH occurred more frequently in women and in the 45-54 year age group, type 1 being the most common.** (Acta gastroenterol. belg., **2009**, 72, **402-406**).

Key words : epidemiology ; hepatitis, autoimmune/diagnosis ; hepatitis, autoimmune/pathology ; hepatitis, autoimmune/drug therapy ; liver cirrhosis.

Introduction

Autoimmune hepatitis (AIH) represents a predominantly periportal and progressive chronic inflammatory liver disease of unknown etiology, usually with hypergammaglobulinemia and tissue autoantibodies, which is responsive to immunosuppressive therapy in most cases (1). There are no features that are pathognomonic of the condition. The marked heterogeneity of AIH with respect to presenting features, severity of disease, and response to therapy has led to several proposals for classification of the disease according to (mainly) immunologic parameters. Type 1 AIH is established in patients positive for antinuclear (ANA) and/or smooth muscle antibodies (SMA), whereas type 2 AIH is diagnosed in patients positive for anti-liver/kidney microsomal antibodies (anti-LKM-1) (1,2). However, the practical usefulness of this classification has been questioned. On the other hand, diagnostic criteria of AIH are based on a scoring system allocating points to different clinical, biochemical, serological, histological, and therapeutic variables recommended by the International Autoimmune Hepatitis Group (IAIHG) in 1993 (3) and revised in 1999 (4).

AIH is a relatively rare disorder, with a preponderance of female patients (male/female ratio 1:4), that can present at any age (although onset in most cases is after 40 years of age). There is little information on the incidence of AIH because on many occasions the disease can progress asymptomatically, diagnostic criteria have changed in the last 20 years, as previously mentioned, and many epidemiological studies have been conducted in retrospective clinical series of patients with AIH. Moreover, the incidence and characteristics of AIH differ in various geographic regions. Based on limited epidemiologic studies, the incidence of type 1 AIH among Caucasoid populations of Europe and North America ranges from 0.1 to 1.9/100,000/year, with important variations according to gender (5-10). The disease is considerably less frequent in Japan. Differences in race and place of origin may modulate the effects of common susceptibility alleles on clinical phenotype by favoring certain etiologic triggers or being associated with genetic polymorphisms that modify the immune response (8).

In order to add further support of epidemiological data in previously published studies of AIH and in a prospective manner, the present study was designed to determine the incidence of AIH in the province of Valencia, Spain, during the year 2003.

Patients and methods

The Services of Gastroenterology of eight acute-care reference hospitals in the province of Valencia, Spain, attending a population of 1,774,736 inhabitants over 14 years of age (856,915 males and 917,821 females) participated in a prospective study. The reference

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population of these centers accounted for 82% of the total population of the province. The study was promoted by the Study Group of Liver Diseases of the Valencian Society of Gastroenterology. A study protocol was designed to collect data prospectively from all patients attended in the participating centers in which a new diagnosis of AIH was made between January 1, 2003 and December 31, 2003. The clinical protocol was approved by the institutional review board of the participating hospitals. All patients gave written consent to undergo liver biopsy.

Diagnosis of AIH was based on criteria recommended by the IAIHG (3,4) (definite AIH > 15 scores before treatment and > 17 after treatment ; probable AIH 10-15 before treatment and 12-15 after treatment). The Simplified Scoring System (11) was equally applied. Type 1 AIH was established in patients positive for ANA and/or SMA, and type 2 in patients positive for anti-LKM-1. The diagnosis of AIH required that none of the patients had HBsAg or anti-HCV (4,5). Patients with autoimmune features and suspicion of metabolic etiology (hereditary hemochromatosis, Wilson's disease or alpha-1-antitrypsin deficiency) were excluded. Liver histology specimens were reviewed by an experienced pathologist and specifically looked for characteristic histological features defined by the IAIHG (3,4) (interface hepatitis, lymphoplasmacytic infiltrate, liver cell rosettes, biliary changes, and other changes) and also graded the degree of necroinflammatory activity and liver fibrosis according to criteria of the METAVIR Cooperative Study Group (12). Patients with histological criteria of non-alcoholic steatohepatitis, independently of the IAIHG score were excluded from the study.

Statistical analysis

Data from the clinical protocol were entered into a centralized database. In all cases, patient anonymity was preserved. Analysis of data was performed by an independent statistician using the SPSS statistical software package (version 7.0 for Windows, SPSS Inc., Chicago, IL, USA). The Fisher's exact probability test was used for the analysis of categorical variables and the Mann-Whitney *U* test for the analysis of continuous variables. Statistical significance was set at $P < 0.05$. The incidence rate (new cases per 100,000 inhabitants) during the year 2003 in the population older than 14 years of age, both overall and individually for each sex, was calculated using data extracted from the population census as a reference. The 95% confidence intervals (CIs) for the incidence were calculated by the substitution method, assuming that the number of cases followed a Poisson distribution (Confidence Interval Analysis 2.1.0).

Results

During the study period, a total of 19 patients (18 woman and 1 man) received a new diagnosis of AIH. The ages of the patients ranged between 23 to 73 years, with a mean (standard deviation, SD) age of 54.3 (11.2) years. All patients were Caucasian.

Eleven (57.9%) patients were asymptomatic and the diagnosis was made during workup studies of incidental hypertransaminasemia, 4 (21%) patients presented with non-specific symptoms, and 4 (21%) with acute hepatitis. Pregnancy was identified as a possible trigger factor in two patients. Four patients had other autoimmune disorders (hyperthyroidism, n = 2 ; Sjögren's syndrome, n = 2). One patient had a sister with AIH.

Eighteen (94.7%) patients were of type 1 (ANA positive, n = 16 ; ANA and SMA positive, n = 2) and 1 patient of type 2 (anti-LKM-1 positive). The autoantibody titers were ≥ 1:80 in all the patients, with an average of 1:640 for ANA and 1:160 for SMA and LKM1. Results of main biochemical tests are shown in Table 1.

Liver biopsy was performed in 17 patients. In the remaining two patients, the liver was not biopsied because the diagnosis of AIH was made during the first trimester of pregnancy (n = 1) and the presence of cirrhosis according to clinical manifestations, results of liver function tests, and echographic findings (n = 1). The histopathological results are shown in Table 2. The grade of activity was moderate or serious (A2-A3) in 59% of cases, and significant hepatic fibrosis was observed (F2-F3-F4) in 47%. In 4 patients (21.1%) cirrhosis was present at the time of diagnosis.

Before treatment, there were 2 IAIHG-classified as probable cases (13 and 15 points), and 17 definitive (4 with 16, 6 with 17, 4 with 18 and 2 with 19 points). After treatment one of he probable case became definitive and the rest remained the same. According to the Simplified Scoring System (17 cases), 2 cases had fewer than 6 points, 2 were probable (6 points) and 13 definitive (9 had 7 and 4 had 8 points).

We have 5-year follow-up data in 17 of 19 cases. No treatment was indicated in 7 cases (5 for minimal alterations of inflammatory and analytical index and absence of symptoms, 1 for descompensated cirrhosis and 1 for comorbidity likely to worsen with treatment. Remision was achieved in the remaining 10 cases (6 with prednisone and 4 with prednisone and azathioprine). In 3 cases medication was withdrawn after 2 years and re-established between 8 and 14 months later due to elevated transaminases.

Incidence of AIH

In the population older than 14 years of age, the incidence of AIH for the year 2003 was 1.07 new cases per 100,000 inhabitants (95% CI 0.64 to 1.67), with an incidence of 1.96 new cases per 100,000 inhabitants (95% CI 1.16 to 3.11) in women and 0.12 new cases per 100,000 inhabitants (95% CI 0 to 0.67) in men. The incidence in females was significantly higher than in males, with a relative risk of 16.81 (95% CI 2.24 to 25.89).

Table 1. — **Biochemical tests**

Serum concentration	Mean ± standard deviation (range)
Aspartate aminotransferase, IU/L	20.9 ± 40.3 (0.8-156.1)
Alanine aminotransferase, IU/L	19.8 ± 28.7 (0.6-100.1)
Alkaline phosphatase, IU/L	1.9 ± 2.3 (0.4-10.1)
Gamma-glutamyl transpeptidase, IU/L	4.2 ± 4.1 (0.7-15.1)
Gamma-globulins, mg/dL	1.4 ± 0.5 (0.7-2.6)
IgG, mg/dL	1.3 ± 0.6 (0.6-2.4)
Bilirubin, mg/dL	3.9 ± 5.9 (0.4-20.0)
Albumin, g/dL	3.9 ± 0.3 (3.1-4.3)
Prothrombin time, %	86 ± 19 (34-120)

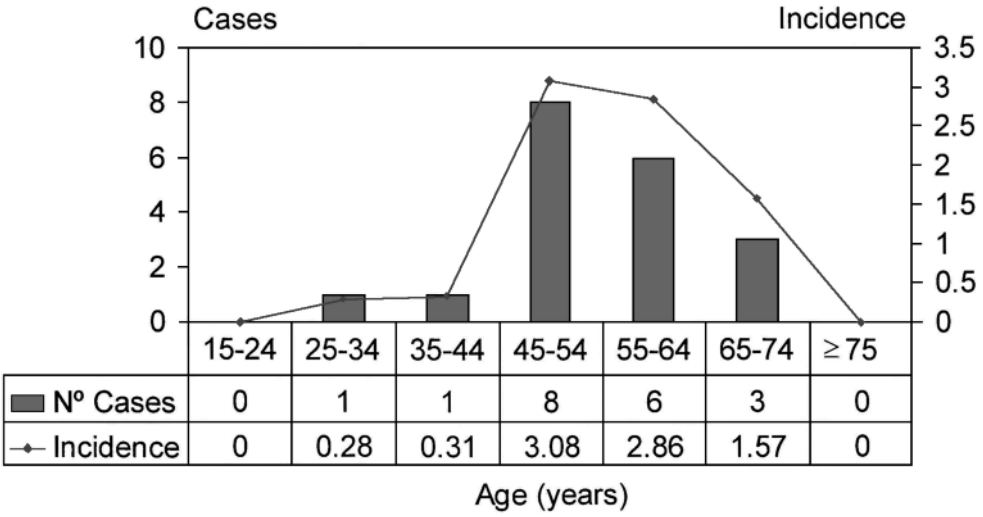

Fig. 1. — Number of cases and incidence (new cases/100,000 inhabitants) in the year 2003, distributed by age groups

Table 2. — **Histological results**

Histology	Number of patients (%)
Activity grade	
A0	2 (11.8)
A1	5 (29.4)
A2	8 (47.1)
A3	2 (11.8)
Fibrosis stage	
F0	3 (17.6)
F1	6 (35.3)
F2	2 (11.8)
F3	3 (17.6)
F4	3 (17.6)

By age, the maximum incidence was observed in the 45-54 year-old age group (3.08 cases per 100,000 inhabitants). The distribution of cases and the incidence by age group is shown in Figure 1. Patients with type 1 AIH showed a higher incidence than patients with type 2 (1.01 cases per 100,000 inhabitants [95% CI 0.6 to 1.61] *vs.* 0.06 cases per 100,000 inhabitants [95% CI 0 to 0.32]).

Discussion

The annual incidence of AIH in the population of the province of Valencia (Eastern Spain on the Mediterranean Sea) older than 14 years of age was 1.07 per 100,000 inhabitants. Because the area covered by the eight participating hospitals accounts for 82% of the total population, the results can be extrapolated to the entire population of our geographical area. As shown in Table 3, the incidence found in the present study is in agreement with previous reports (5-7,13-21), although it should be noted that in studies carried out prior to 1993, the year at which initial IAIHG diagnostic recommendations were published, consistent diagnostic criteria of AIH were lacking.

The diagnosis of AIH was based on IAIHG[3,4] consensus criteria, which requires exclusion of viral, drug induced, alcoholic, and hereditary liver disease (22). The purity of the sample and the exclusion of other underlying liver diseases is a strength of the study. Moreover, there are liver biopsy data for most patients. It has been shown that the AIH score without liver biopsy findings is not useful for diagnosing AIH in patients with nonalcoholic fatty liver disease (23). In HCV-infected patients,

Table 3. — **Incidence and prevalence data of autoimmune hepatitis in different areas**

Reference	Study period	Area	Inhabitants	No. cases	Incidence*	Prevalence†
14	1970-1979	Iceland	225,000	25	0.83	8
15	1976-1980	UK	404,000	14	0.69	
16	1981	Norway	4,100,000	49	1.10	
17	1979-1985	Sweden	2,700,000	206	0.85	
18	1971-1987	UK	210,000	20	0.60	
19	1985-1994	Norway		29	1.6	14
8	1986-1995	Norway	130,000	25	1.9	16.9
20	1990-1996	Singapore	567,685	24	0.60	3.3
21	1984-2000	Alaska	100,312	49		42.9
Current series	2003	Valencia, Spain	1,774,736	19	1.07‡	

* New cases per 100,000 inhabitants.
† Cases per 100,000 inhabitants.
‡ Rates refer to 100,000 inhabitants older than 14 years of age.

ANA and ASM antibodies are frequently found. Antibodies to LMK-1, a marker for AIH type 2 are also found in patients with HCV infection (24-26). However, the differentiation between HCV infection and AIH is not difficult due the availability of diagnostic viral markers.

In our experience, and coincideng with Búchel *et al.* (25) pregnancy often improves the clinical and laboratory AIH, but in this group AIH was present in one case and deteriorated in the other, during pregnancy.

In our study like others (27,28), AIH occurred more frequently in women than in men. Relevant findings of this study include older age at presentation and more asymptomatic patients than expected. More than 50% of patients had no clinical manifestations (jaundice, pruritus or other symptoms) and were referred to a specialized unit for the study of elevated serum aminotransferase levels detected incidentally on a routine laboratory investigation for other reasons. These findings correspond to the histological lesions of low grades of inflammatory activity and stage of fibrosis observed in half of the cases. All these observations lead us to assume that the greater part of AIH patients in our region develops less aggressive forms than those described in the majority of other studies. In addition, the prospective nature of the study may also account for this finding. Earlier detection and treatment of AIH is likely to alter the natural history of the disease.

In summary, the 2003 annual incidence of AIH in subjects older than 14 years of age in the province of Valencia (Spain) was 1.07 per 100,000 inhabitants, which is similar to that reported in other European countries. AIH occurred more frequently in women and in the 45-54 year age group, being type 1 the most common. The diagnosis of AIH should always be considered in the work-up studies of patients with persistently raised aminotransferases or presenting with acute hepatitis.

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References

1. MC FARLANE I.G. Definition and classification of autoimmune hepatitis. *Semin. Liver Dis.*, 2002, **22** : 317-24.
2. CZAJA A.J., FREESE D.K. Diagnosis and treatment of autoimmune hepatitis. *Hepatology*, 2002, **36** : 479-97.
3. JOHNSON P.J, MC FARLANE I.G. Meeting Report : International Autoimmune Hepatitis Group. *Hepatology*, 1993, **18** : 998-1005.
4. ALVAREZ F., BERG P.A., BIANCHI F.B., BIANCHI L., BURROUGHS A.K., CANCADO E.L., CHAPMAN R.W., COOKSLEY W.G., CZAJA A.J., DESMET V.J., DONALDSON P.T., EDDLESTON A.L., FAINBOIM L., HEATHCOTE J., HOMBERG J.C., HOOFNAGLE J.H., KAKUMU S., KRAWITT E.L., MACKAY I.R., MACSWEEN R.N., MADDREY W.C., MANNS M.P., MC FARLANE I.G., MEYER ZUM BÜSCHENFELDE K.H., MIELI-VERGANI G., NAKANUMA Y., NISHIOKA M., PENNER E., PORTA G., PORTMANN B.C., REED W.D., RODÈS J., SCHALM S.W., SCHEURER P.J., SCHRUMPF E., SEKI T., TODA G., TSUJI T., TYGSTRUP N., VERGANI D., ZENIYA M. International Autoimmune Hepatitis Group Report : review of criteria for diagnosis of autoimmune hepatitis. *J. Hepatol.*, 1999, **31** : 929-38.
5. VERGANI D., GREGORIO G.V., CHOUDHURI K., MA Y., VEGNENTE A., MIELI.VERGANI G. Hepatitis virus induced autoimmunity. *Acta Gastroenterol. Belg.*, 1998, **61** : 217.
6. BOBERG K.M. Prevalence and epidemiology of autoimmune hepatitis. *Clin. Liver Dis.*, 2002, **6** : 347-59.
7. BOBERG K.M., AADLAND E., JAHNSEN J., RAKNERUD N., STIRIS M., BELL H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand. J. Gastroenterol.*, 1998, **33** : 99-103.
8. CZAJA A.J. Autoimmune liver disease. *Curr. Opin. Gastroenterol.*, 2006, **22** : 234-40.
9. CINDORUK M, YETKIN I, KARAKAN T., KANDILCI U. The prevalence of autoimmune hepatitis in Hashimoto thyroiditis in a Turkish population. *Acta Gastoenterol. Belg.*, 2002, **65** : 143-145.
10. HENNES E.M., ZENIYA M., CZAJA A.J., PARÉS A., DALEKOS G.N., KRAWITT E.L., BITTENCOURT P.L., PORTA G., BOBERG K.M., HOFER H., BIANCHI F.B., SHIBATA M., SCHRAMM C., EISENMANN DE TORRES B., GALLE P.R., MC FARLANE I., DIENES H.P., LOHSE A.W., INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP. Simplified criteria for the diagnosis of Autoimmune Hepatitis. *Hepatology*, 2008, **48** : 169-176.
11. BEDOSSA P., POYNARD T. FOR THE METAVIR COOPERATIVE STUDY GROUP. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology*, 1996, **24** : 289-93.
12. COTLER S.J., KANJI K., KESHAVARZIAN A., JENSEN D.M., JAKATE S. Prevalence and significance of autoantibodies in patients with non-alcoholic steatohepatitis. *J. Clin. Gastroenterol.*, 2004, **38** : 801-4.
13. BJARNASON I., MAGNÚSSON B., BJÖRNSSON S. Idiopathic chronic active hepatitis in Iceland. An epidemiological study. *Acta Med. Scand.*, 1982, **211** : 305-7.
14. HODGES J.R., MILLWARD-SADLER G.H., WRIGHT R. Chronic active hepatitis : the spectrum of disease. *Lancet*, 1982, **1** : 550-2.
15. RITLAND S. The incidence of chronic active hepatitis in Norway. A retrospective study. *Scand. J. Gastroenterol. Suppl.*, 1985, **107** : 58-60.

16. OLSSON R., LINDBERG J., WEILAND O., NILSSON L. Chronic active hepatitis in Sweden. The etiologic spectrum, clinical presentation and laboratory profile. *Scand. J. Gastroenterol.*, 1988, **23** : 463-70.
17. TANNER A.R., DELLIPIANI A.W. Chronic active hepatitis : a sixteen-year survey at a district general hospital. *Postgrad. Med. J.*, 1989, **65** : 725-8.
18. BERDAL J.E., EBBESEN J., RYDNING A. Incidence and prevalence of autoimmune liver disease. [Article in Norwegian]. *Tidsskr. Nor Laegeforen*, 1998, **118** : 4517-9.
19. LEE Y.M., TEO E.K., NG T.M., KHOR C., FOCK K.M. Autoimmune hepatitis in Singapore : a rare syndrome affecting middle-aged women. *J. Gastroenterol. Hepatol.*, 2001, **16** : 1384-9.
20. HURLBURT K.J., MC MAHON B.J., DEUBNER H., HSU-TRAWINSKI B., WILLIAMS J.L., KOWDLEY K.V. Prevalence of autoimmune liver disease in Alaska natives. *Am. J. Gastroenterol.*, 2002, **97** : 2402-7.
21. BEN-ARI Z., CZAJA A.J. Autoimmune hepatitis and its variant syndromes. *Gut*, 2001, **49** : 589-94.
22. YATSUJI S., HASHIMOTO E., KANEDAL H., TANIAI M., TOKUSHIGEL K., SHIRATORI K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease : is the International Autoimmune Hepatitis Group scoring system useful ? *J. Gastroenterol.*, 2005, **40** : 1130-8.
23. STRASSBURG C.P., VOGEL A., MANNS M.P. Autoimmunity and hepatitis C. *Autoimmun. Rev.*, 2003, 2 : 322-31.
24. CASSANI F., CATALETA M., VALENTINI P., MURATORI P., GIOSTRA F., FRANCESCONI R., MURATORI L., LENZI M., BIANCHI G., ZAULI D., BIANCHI F.B. Serum autoantibodies in chronic hepatitis C : comparison with autoimmune hepatitis and impact on the disease profile. *Hepatology*, 1997, **26** : 561-6.
25. BÜCHEL E., VAN STEENBERGEN W., NEVENS F., FEVERY J. Improvement of autoimmune hepatitis during pregnancy followed by flare-up delivery. *Am. J. Gastronterol.*, 2002, **97** : 3160-5
26. CZAJA A.J., MAGRIN S., FABIANO C., FIORENTINO G., DIQUATTRO O., CRAXI A., PAGLIARO L. Hepatitis C virus infection as a determinant of behavior in type 1 autoimmune hepatitis. *Dig. Dis. Sci.*, 1995, **40** : 33-40.
27. FELD J.J., HEATHCOTE E.J. Epidemiology of autoimmune liver disease. *J. Gastroenterol. Hepatol.*, 2003, **18** : 1118-28.