

Epidemiology of chronic autoimmune liver disease: A histopathological study in third-level hospital in Mexico City

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RESUMEN

Introducción. Las enfermedades hepáticas autoinmunes (EHAI) comprenden un grupo heterogéneo. Las frecuencias relativas de las EHAI no se han estudiado adecuadamente. Los estudios epidemiológicos en México son limitados. **Objetivo.** El objetivo es determinar la prevalencia de histopatología compatible con EHAI en un grupo de pacientes mexicanos. **Material y métodos.** Se examinaron retrospectivamente 785 biopsias hepáticas. Se analizaron los expedientes clínicos para la recolección de datos. **Resultados.** Sesenta y siete pacientes mostraron características compatibles con EHAI; 56 mujeres (83.6%) y 11 hombres (16.4%). Los resultados mostraron que la prevalencia de EHAI durante este periodo fue de 8.5%. La comorbilidad frecuentemente asociada fueron otras enfermedades autoinmunes (20.89%). La principal causa de cirrosis en el grupo de mujeres fue hepatitis autoinmune (100%) y en el grupo de hombres fue colangitis biliar primaria (42%). **Conclusiones.** Este estudio muestra una probable tendencia en aumento de la prevalencia de EHAI; sin embargo, es importante recolectar más información epidemiológica para determinar la verdadera prevalencia.

Palabras clave. Hepatitis autoinmune. Colangitis. Esclerosante. Biopsias. Hígado. Prevalencia.

ABSTRACT

Background. Autoimmune liver diseases (AILD) comprise a heterogeneous group. The relative frequencies of AILD have not been studied properly. Epidemiological studies in Mexico are limited. **Objective.** The aim was to determine the prevalence of AILD histopathology in a group of Mexican patients. **Material and methods.** We retrospectively examined 785 liver biopsy specimens. Medical records were analyzed in order to recollect data. **Results.** Sixty-seven patients showed compatible characteristics with AILD; 56 were women (83.6%) and 11 men (16.4%). The results showed that the prevalence of AILD during this period was 8.5%. The most frequent associated comorbidity was other autoimmune diseases (20.89%). The main cause of cirrhosis in the female group was AIH (100%), and in the male group PBC (42%). **Conclusions.** This study shows a probable increasing tendency in the prevalence of AILD, however, it is important to collect more epidemiological information in order to truly define the prevalence.

Key words. Hepatitis. Autoimmune. Cholangitis. Sclerosing. Liver. Biopsy. Prevalence.

INTRODUCTION

The group of autoimmune liver diseases (AILD) comprises autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and a recently discovered entity, an immunoglobulin G4-associated cholangitis (IAC). These, in turn, are classified depending on the target cell affected: hepatocyte or biliary epithelium. The hepatocellular damage characterizes the AIH; on the contrary, cholangiopathies in-

clude PBC and PSC. There are a proportion of patients exhibiting features of two different AILD, designated as an overlap syndrome (OS), subdivided into 3 types: AIH-PBC, AIH-PSC and PBC-PSC.¹ The precise pathogenesis of AILD is poorly understood and includes an association of environmental, genetic and immunological factors. All types of AILD are characterized by a varying degree of immune-mediated liver injury and by a strong association with human leukocyte antigen (HLA). Despite sharing a common autoimmune pathogenesis, the

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AILD are characterized by fairly distinct demographic patterns of disease.²

The relative frequencies of AILD have not been studied properly. Epidemiological studies in Mexico are limited and scarce. A recent study projected the trends in liver disease prevalence to 2,050 based on mortality data; alcohol etiology will be accounting for 996,225 cases in 2050; no data regarding AILD appeared to be significant.³ A multicenter study with a national sample of 1,486 liver cirrhosis patients confirmed that alcohol and hepatitis C were the main causes; PBC first appeared as a secondary cause with a 5.7%.⁴ Frequently data from other countries is extrapolated to a population with different demographic characteristics, not truly reflecting the prevalence of the disease. Globally, the vast majority of studies have focused on PBC; perhaps as a result of these, it is the subtype with the most variation in incidence rates. Jepsen, *et al.*⁵ systematically reviewed 55 studies on the incidence of AILD in general population, only 14 (25%) of them used a standard population.⁵ Specifically, studies of PBC covering the years before 1985 tend to find incidence rates around 1 per 100,000 annually mainly in European populations. Since then, studies from North England have found even higher incidence rates, 4.33 per 100,000 per year in New Castle, England.⁶ No studies have found higher incidence rates of PBC than in the ones conducted in England. Meanwhile, 17 studies described the population incidence of AIH. The process of identifying AIH patients is more complex and the diagnostic criteria are unclear in the majority of studies. The highest incidence 3 per 100,000 person-years was found in West Suffolk, England.⁷ Finally, 14 studies identified PSC population. The highest incidence, 2 per 100,000 person-years in 2003-2004 was found in West Suffolk,⁷ and at the other end of the spectrum, none of 100,000 Alaska natives were diagnosed during 1984 to 2008. No studies examined the population incidence of IAC. Most of the epidemiological studies have been conducted very differently, and therefore, it is difficult to determine whether incidence varies because of differences in methods or because of different risk factors associated.⁵ Further, there was not a single Latin American epidemiological study addressing these issues, and only a few in the United States population.

The diagnosis of AILD requires the exclusion of other causes of liver damage, as well as a careful evaluation of clinical, biochemical, histopathological, and cholangiographic characteristics specific to each of the major AILD entities. Although few of these disease features are individually diagnosed, particular combinations are needed for a high sensitivity and specificity criteria, area in which fur-

ther development is needed.⁹ Moreover, liver biopsy has been the gold standard for diagnosing liver disease; however with the development of diagnostic testing, novel autoantibodies and noninvasive assessment of liver fibrosis existing indications are limited. According to the AASLD, liver biopsy currently has three major roles: 1) diagnosis, 2) assessment of prognosis (disease staging), and/or 3) assistance in making therapeutic management decisions.¹⁰ Liver histology is commonly used in disease monitoring of patients with AIH, mainly because of the different histological presentations. Predominant or exclusive centrilobular injury is now recognized in the histological spectrum of AIH and may represent an early stage of the disease.¹¹ There is evidence that patients with PBC and advanced fibrosis on biopsy at diagnosis may respond less well to ursodeoxycholic acid than do patients with minimal or mild fibrosis, thus placing them at risk of more rapid disease progression and premature death/requirement for liver transplantation.¹² Furthermore, in patients with chronic liver disease, liver biopsy was required in 7.2%, but in 31.2% of cases, it can change the diagnosis.¹³

The aim of this study was to determine the prevalence of positive autoimmune liver disease histopathology in a group of Mexican patients. The second aim was to characterize the clinicopathological features and describe the spectrum of morphological findings of AILD.

MATERIAL AND METHODS

A retrospective study was conducted. We used the pathology records of seven hundred eighty-five liver biopsy specimens between the years 2008 and 2013. Of these, sixty-seven patients showed compatible histopathological characteristics with AILD. Liver biopsies were performed on an outpatient basis or by direct ultrasound guided biopsy. The choice of method was left to the attending physician. Formalin-fixed paraffin-embedded sections were stained with H/E, periodic acid-Schiff, and Masson's trichome stain. A semi-quantitative 4-grade system (absent, minimal, moderate, and severe) was used to assess histologic parameters such as portal inflammation, lymphocytic aggregates in portal tracts, piecemeal necrosis, and spotty lobular necrosis. Fibrosis was graded as portal, bridging, or cirrhosis. Two pathologists who were blinded to the clinical and serologic data performed the histologic evaluation. We reviewed the medical records of all 67 patients who had histopathological characteristics compatible with AILD. Data on demographics such as age, sex, and place of birth were obtained; as well as clinical data such as alcohol and cigarette consumption. Finally, biochemical

and immunological data was sought. Liver autoantibodies including antinuclear antibodies (ANA), smooth muscle antibody (SMA), liver kidney microsomal antibody type 1 (LKM1), and antimitochondrial antibodies (AMA). AIH was suspected when immunoglobulin type G (IgG) was elevated and/or when autoantibodies ANA, SMA, LKM1 were present. PBC was suspected in the presence of cholestatic enzyme pattern and positive AMA. PSC was suspected in the presence of cholestatic enzyme pattern, negative AMA and bile duct abnormalities with multifocal strictures and segmental dilatations in magnetic resonance cholangiopancreatography or endoscopic cholangiopancreatography. We calculated the prevalence in the period of 6 years, and then the point prevalence for each year of biopsies analysis.

RESULTS

Of the seven hundred eighty-five ($n = 785$) liver biopsy specimens, only sixty-seven patients ($n = 67$) had a positive histopathology compatible with AILD by the following diagnosis: AIH ($n = 38$), PBC ($n = 17$), PSC ($n = 1$), OS ($n = 11$) (Figure 1); 56 were women (83.6%) and 11 men (16.4%). The average age in the female group was 49.5 years (19-73 years), and in the male group, 52 years (28-72 years).

The results showed that the prevalence of positive histopathology of AILD in liver biopsies during the period of six years was 8.5% (Figure 2). The distribution of place of birth was as follow: 32 patients were born in Mexico City (47.76%), 16 patients in Estado de México (23.88%) the rest were distributed among different states. In 8 patients no data could be obtained from alcohol and cigarette consumption;

from the rest, 28 patients (41.79%) had positive cigarette consumption and 31 (46.26%) had negative consumption; 26 (38.80%) patients consumed alcohol (< 40 g/day), and 41 (61.19%) had never consumed it.

Only 46 of 67 patients (68.65%) display complete biochemical laboratories. Patients with PBC exhibit a predominant cholestatic pattern, characterized by higher levels of alkaline phosphatase and gamma glutamyl transpeptidase (Table 1). Concerning histopathological findings, portal inflammation was present in all the patients (100%), regardless AILD subtype. Granulomas were present in 1 (2.6%), 1 (9.1%), and 2 (11.8%) of AIH, OS and PBC liver biopsy specimens, respectively. Biliary lesions and duct loss were more prominent in PBC and OS than in AIH, relevant to this, cholestasis was also a characteristic feature in PBC (41.2%). Features of hepatocellular damage such as focal or spotty necrosis were seen frequently in AIH and OS; none of the patients presented confluent necrosis. Interface hepatitis (piecemeal necrosis) was predominantly in OS (90.9%) while AIH and PBC had a similar presentation, 16 (42.1%) and 7 (41.2%) respectively. PBC showed a consistent low-grade portal fibrosis (F1-2), while cirrhosis was more prominent in the OS group (36.4%). AILD cases showed a low-grade level of steatosis, mainly grade 1 or less. Main histopathological findings are summarized in table 2.

The most frequent associated comorbidity were other autoimmune diseases (20.89%), mainly systemic lupus erythematosus, ankylosing spondylitis and Sjogren syndrome. Smoking was present in 28 patients (41.79%) and alcohol consumption in 32 (47.7%) (Table 3). The main cause of cirrhosis in the female group with the established

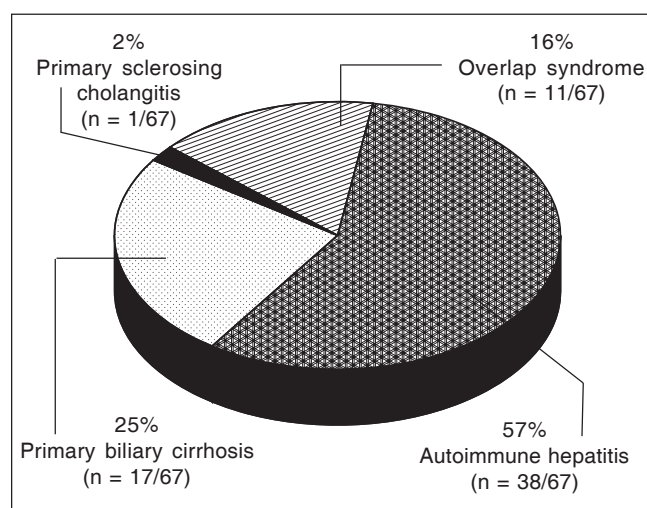


Figure 1. Distribution of subtypes of autoimmune liver diseases.

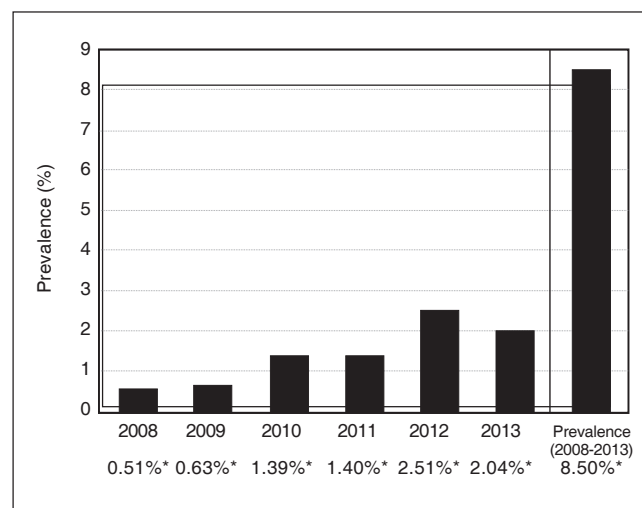


Figure 2. Point prevalence* distribution of autoimmune liver diseases.

Table 1. Main laboratory parameters in the different diagnostic groups (median and range are given).

Histopathol. diag.	N	Hb (g/dL)	Pla (mill/mm ³)	Glob (g/dL)	ALT (UI/L)	AST (UI/L)	BT (mg/dL)	Alk. P (UI/L)	γ-GT (UI/L)	Alb (g/dL)
AIH (n = 38)	27	14 (7.3-16.8)	223 (57-395)	3.3 (2.2-4.8)	98.5 (15-1284)	76 (20-1061)	1.09 (.43-6.62)	95 (11-537)	159 (11-625)	3.55 (1.86-5)
PBC (n = 17)	11	12.2 (6.5-15.6)	202 (135-469)	2.5 (2.3-5.1)	47 (21-160)	53 (30-168)	0.98 (.7-5)	232 (70-1190)	96 (26-1024)	3.8 (2-4.9)
OS (n = 11)	8	14.1 (13.3- 15.1)	259 (206-375)	3.1 (2.6-3.7)	91 (39-208)	162 (40-142)	1.1 (.49-3.3)	249 (41-641)	319 (29-1020)	3.8 (2.9-4.3)

Histopathol. diag.: Histopathological diagnosis N: number of patients with complete laboratory findings. Hb: hemoglobin. Pla: platelets. Glob: globulins. ALT: alanine aminotransferase. AST: aspartate aminotransferase. BT: total bilirubin. Alk P: alkaline phosphatase. γ-GT: gamma glutamil transpeptidase. Alb: albumin.

diagnosis of autoimmune liver disease was AIH (100%); and in the male group PBC (42%). In this series, there were no major complications associated with the liver biopsy procedure.

DISCUSSION

In the present retrospective study, the prevalence of positive AILD histopathology in the period of six years was 8.5%. A tendency in increasing prevalence is observed throughout the years, confirming similar results around the world. Between 1987-1994, prevalence rates in the United Kingdom increased significantly from 14.9 to 25.1 cases per 100,000 population ($p < 0.00001$).¹⁴ In the case of AIH, it is noteworthy the increasing incidence in a Danish population with about 0.3 to 0.4 cases per 100,000 population higher between the years 1994-2012, although the population was not standardized.¹⁵ It is important not to ignore a possible regional variation that could explain the increasing trend. Other findings such as female predominance and an average age of presentation between 49.5 and 52 years old are consistent with the literature. There are few studies examining using liver biopsy as a determinant key in its diagnosis. A similar study published by Terraciano, *et al.*,¹⁶ examined 42 liver biopsies from patients with histological criteria of ALD. The distribution of the entities was significantly different: 10 cases of OS, 10 of IAC, 10 of PBC and 9 of AIH.¹⁶ Similar to our study, the minority of cases or even none of PSC cases were diagnosed by histopathology characteristics, emphasizing the fact that diagnosis of PBC is made with bile duct changes seen on an imaging study along with a cholestatic pattern. The high number of patients that underwent liver biopsy as an outpatient manner could explain the minimum shortage of autoantibodies. Moreover, specific serology has proved to be a mainstay of diagnostic testing in

AIH and PBC, but a disease-relevant reactant has not been identified in PSC.⁹ Autoantibody titres usually vary during the course of the disease. Hence, seronegativity, low or high autoantibody titres on a single test cannot exclude the diagnosis of AILD⁹ when approaching a patient with AILD a complete biochemical, serological, clinical and/or histological characteristics are required. The vast majorities of epidemiological studies of ALD are marked with heterogeneity in the study design, and lack information to determine an accurate diagnosis. To improve the standardization and accuracy of future epidemiological studies of AILD, Metcalf and James⁶ proposed a set of specific guidelines to be followed:

- Stringent case inclusion criteria.
- Clear definition of date of disease onset.
- Well defined study period, area and population.
- Multiple case-finding methods.
- Rigorous tracing of all available information and possible cases.⁶

More work is needed to be done to regulate the use of more data sources such as searches of liver biopsy, immunology, laboratory or even autopsy databases to identify patients. The benefits of epidemiological data are well studied; the advances made in the understanding of the definition and pathogenesis of these complex diseases is the most significant contribution. These studies provide information that is important not only to our patients, but also to healthcare administrators who must dimension our outpatient clinics and even to pharmaceutical companies who plan experimental studies.⁵ Finally, the information given by this type of studies may enable to estimate the number of liver transplantations required due to AILD.

The specific value of isolated liver biopsy in AILD remains unanswered. Histology is often considered to be a

Table 2. Histological findings.*

	AIH (n = 38)	OS (n = 11)	PBC (n = 17)	PSC (n = 1)
1. Portal inflammation	38 (100%)	11 (100%)	17 (100%)	1 (100%)
2. Bile duct lesions	9 (23.7%)	9 (81.8%)	15 (88.2%)	1 (100%)
3. Bile duct loss	2 (5.3%)	2 (18.2%)	3 (17.6%)	0 (0%)
4. Nodular lymphocytic aggregates or germinal centers	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)
5. Focal or spotty lobular necrosis	6 (15.8%)	2 (18.2%)	1 (5.9%)	0 (0%)
6. Confluent necrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7. Piecemeal necrosis (interface hepatitis)	16 (42.1%)	10 (90.9%)	7 (41.2%)	0 (0%)
8. Portal fibrosis (F1-2)	6 (15.8%)	4 (36.4%)	6 (35.3%)	0 (0%)
9. Bridging fibrosis (F3)	5 (13.2%)	0 (0%)	1 (100%)	0 (0%)
10. Cirrhosis (F4)	9 (23.7%)	4 (36.4%)	5 (29.4%)	0 (0%)
11. Granulomas	1 (2.6%)	1 (9.1%)	2 (11.8%)	1 (100%)
12. Steatosis (grades 1-3)**	7 (18.4%)	2 (18.2%)	9 (52.9%)	0 (0%)
13. Cholestasis	2 (5.3%)	2 (18.2%)	7 (41.2%)	1 (100%)

AIH: autoimmune hepatitis. OS: overlap syndrome. PBC: primary biliary cholangitis. PSC: primary sclerosing cholangitis. * Data are given as number (%) of biopsy specimens with moderate or severe findings. ** Steatosis was mainly grade 1 or less.

Table 3. Disease associations of autoimmune liver disease.

Primary biliary cirrhosis (n = 17)	Autoimmune hepatitis (n = 38)	Overlap syndrome (n = 11)
Systemic lupus erythematosus	Rheumatoid arthritis	Sjögren's syndrome
Sjögren's syndrome	Ulcerative colitis	
Rheumatoid arthritis	Ankylosing spondylitis	
Liquen planus	Systemic lupus erythematosus	
	Graves' disease	
	Lymphocytic colitis	

gold standard in many aspects of the diagnosis. However, there is an acknowledgment that diagnostic errors can occur, and that intra- and inter-observer variation may be considerable;¹⁷ the yield is particularly high in marker negative patients.¹⁸ In a recent study of histopathological diagnosis of 1,265 liver biopsies, differences in histopathological interpretation were present in 59% biopsies and 67% were predicted at the time to impact on patient management; diagnostic differences occurred in 70% of biliary disease, autoimmune hepatitis, and vascular changes.¹⁷ The differential diagnosis between ALD remains a challenging problem, so this study could suggest that biopsies in ALD should be reviewed not only by the pathologist but also by a liver specialist to reduce misunderstanding in the diagnosis. To emphasize this point, it is well known that the key histologic features of AIH are a chronic hepatitis pattern of injury with portal and periportal lymphoplasmacytic infiltrates, interface hepatitis, a not prominent bile destruction and a severity of necro-inflammatory activity quite variable. Our data confirms these observations and others regarding that this histologic pattern of injury may be indistinguishable from PBC. The PBC cases in our study demonstrate a mild bile duct injuries

and a low bile duct loss. Recent studies have shown that the diagnostic accuracy of PBC cases depends on the bile duct injury; in cases with severe bile duct injuries the accuracy is very high (over 80%), while the accuracy in mild bile duct injuries lowers to a 50% or less.¹⁹ Another problem in PBC cases is that the differential diagnosis depends on the stage of the disease. The high number of cases with interface hepatitis and cholestasis in our PBC group could be explained by the fact that these cases were detected in advanced stages 2 or 3 of the disease, coupled with the presence of portal fibrosis in this group. The value of histologic staging in assessing prognosis in early-stage PBC is debatable, given the lack of uniformity of duct loss in the liver disease.²⁰ These data confirm recent observations showing the lack of substantial histologic differences between AIH and PBC, so other diagnostic tools like clinical and serological markers should be used. In cases of PSC, liver biopsy is undertaken to rule out other causes but not as a diagnostic tool, demonstrated by the low prevalence of this subtype in our study. The OS was first described in 1997, is an uncommon chronic liver disease with morphologic, serologic and clinical features of both PBC and AIH.¹⁶ While moderate and severe bile duct

lesions were present in 80%, bile loss was only present in less than 20%, granulomas were seen in 2 patients (20%) and the typical hepatitis features such as lobular necrosis, piecemeal necrosis were found in 5.9 and 41.2% respectively. These data suggest that the histologic features of OS are closer to AIH than to PBC.

The present study has some limitations. First, this was a retrospective observational study. Second, sampling error and histopathological analysis done only by one pathologist are factors that limit diagnostic accuracy. Finally, although our biopsy sample was large, we cannot overlook the fact that more than half of the patients (68.65%) lack complete biochemical laboratories and only 6 of 67 (8.95%) had specific autoantibodies.

In conclusion, the group of AILD is a complex and varied group of entities. When managing a patient with AILD, a long term and stratified approach to care must be adopted; a focus on clinical, serological, and histopathological characteristics is essential in determining with accuracy a definitive diagnosis. Nowadays, there is a large shortfall of epidemiological studies in certain populations, including Mexico. Thus, further rigorous studies are needed to truly define the incidence, prevalence, familial risk and disease associations in this entity.

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