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Original Research

Diagnosis and Treatment of Autoimmune Liver Diseases in a Tertiary Referral Center in Cuba

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ABSTRACT

Background: Autoimmune liver diseases (AILD) comprise a set of entities characterized by tissue damage as a result of the loss of self-tolerance. There are few reports of AILD from Caribbean countries.
Objectives: The aim of our study was to investigate the clinical patterns, laboratory findings, and immunologic features, treatment responses, and prognoses of AILD in adult patients at a Cuban tertiary referral center.
Methods: A prospective study was conducted at the National Institute of Gastroenterology in Havana, Cuba, from May 2012 to April 2016. Clinical, immunologic, and histologic features of autoimmune hepatitis (AIH), primary biliary cirrhosis, AIH/primary biliary cirrhosis overlap syndrome, autoimmune cholangiopathy, and primary sclerosing cholangitis were recorded. Response to therapy was assessed by serum alanine aminotransferase and bilirubin levels at 3, 6, 12, and 24 months after treatment initiation.
Results: Of the 106 patients included in the study, 85.5% were women. The median age at presentation was 47 years. AIH was the most common AILD and was diagnosed in 60 patients (56.6%), 55 of whom had type 1 AIH. Primary biliary cirrhosis was diagnosed in 22 patients (20.7%), overlap syndrome in 16 patients (15%), autoimmune cholangiopathy in 5 patients (4.71%), and PSC in 3 patients (2.8%). Most patients were symptomatic; 48 patients (45.2%) presented with liver cirrhosis, 14.5% of whom had decompensated cirrhosis. Follow-up of treatment was between 6 and 24 months. Prednisone monotherapy was used in 22 AIH patients (36.6%) and a combination of prednisone and azathioprine was used in 28 (46.6%) AIH patients. Response to treatment was seen in 41 AIH patients (68.3%), 33 of whom (55%) had a complete response and 8 of whom (24.2%) relapsed after 12 months of maintenance therapy. No or incomplete response to treatment was seen in 18 patients (30%). In 46 patients with autoimmune cholestasis, ursodeoxycholic acid was used as monotherapy in 25 patients (54.3%).
Conclusions: The clinical profile of AILD in a sample of the Cuban population is similar to that reported in South areas (Developing countries). AIH was more frequent than PBC, and usually presented with advanced liver disease that responded poorly to treatment.

Introduction

Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune cholagniopathy (AIC), comprise a set of entities characterized by tissue damage as a result of the loss of self-tolerance, often in genetically susceptible individuals. These entities sometimes co-occur or overlap, making it difficult to establish conclusive diagnostic criteria and raising the question of whether they are distinct diseases or variants within a spectrum.[1,2] AILDs have a low prevalence relative to other liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. Genetic, cultural, environmental, social, racial, and other differences across various geographic regions may be involved in the expression of AILD.[3]

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AILD diagnosis is based on histologic abnormalities, clinical and laboratory findings, and the presence of 1 or more characteristic autoantibodies. In routine clinical practice in developing countries, AILD diagnosis often relies upon clinical, biochemical, and histologic criteria alone, because autoantibody studies are often unavailable.[4] Most AILD prevalence estimates have been based on European and US populations.[5–8] In Cuba and other Caribbean countries, population-based studies of the clinical course, incidence, prevalence, and prognosis of these diseases are scarce.

The aim of this study was to investigate the clinical patterns, laboratory findings, immunologic features, treatment responses, and prognoses of adult patients with AILD treated at a tertiary referral center in Cuba.

Materials and Methods

A prospective study was conducted at the National Institute of Gastroenterology, Havana, Cuba, between May 2012 and April 2016. The study was approved by the institutional ethics committee. Written informed consent was obtained from patients before study enrollment. A total of 8320 adult patients were admitted to the outpatient clinic during the study period. A total of 130 patients were recruited, 106 of whom satisfied the inclusion criteria for their particular diagnosis (**Table I** and **Figure 1**). Six patients with AILD did not meet inclusion criteria. AIH diagnosis was based on the simplified International Autoimmune Hepatitis Group 2008 criteria.[9] The diagnostic criteria for PBC, AIC, and PSC were based on the practice guidelines of the American Association for the Study of Liver Diseases.[7,8] The Chazouillères criteria were used for the diagnosis of AIH/PBC overlap syndrome.[10] Patients were excluded from the analysis if evidence of AILD diagnosis was insufficient or if their medical records were incomplete due to poor follow-up. Exclusion criteria also included pregnancy, HIV infection, hepatitis B or C virus infection, alcohol consumption, use of potentially hepatotoxic drugs, neoplastic disease, and liver ischemic diseases.

All laboratory analyses were performed under the internal organization rules and procedures for the development of clinical trials (Good Clinical Practice), which receive external quality control by the Cuban national regulatory authority, Center for State Control of Medicines, Equipment, and Medical Devices. Patient information was obtained from medical records available from the hepatology department. All patients were evaluated according to the AILD protocol of the Department of Hepatology at National Institute of Gastroenterology.[11]

Study Variables

Mode of Presentation

Patients were categorized into 1 of 4 distinct patterns of AILD presentation: asymptomatic (absence of symptoms with only occasional abnormal liver tests), acute disease (<30 days onset of symptoms, including jaundice, fatigue, drowsiness, or fever, with marked alterations in serum liver function test), insidious onset (mild symptoms of illness for at least 6 months, including progressive fatigue, malaise, anorexia, weight loss, jaundice, or pruritus), or liver cirrhosis (clinical manifestations of established liver cirrhosis). Decompensated cirrhosis was defined as the presence of 1 of the following features: ascites, variceal bleeding, hepatic encephalopathy, bacterial peritonitis, low serum albumin (<35 g/L), and prolonged prothrombin time (>15 seconds).

Concurrent Autoimmune Disorders

We recorded the presence of concurrent arthritis (ie, nonspecific arthralgia with inflammation) or a confirmed diagnosis of other autoimmune diseases (eg, thyroid disease, rheumatoid arthritis, glomerulonephritis, systemic lupus erythematosus, ulcerative colitis, and others).

Table I
Definitions used for each autoimmune liver disease.

Primary biliary cirrhosis[7]	The diagnosis can be established when 2 of the following three criteria are met: ✓ Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation ✓ Presence of AMA ✓ Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
Autoimmune cholangiopathy (AMA-negative PBC)[7]	✓ Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation ✓ Histologic evidence of nonsuppurative destructive cholangitis, presence of granulomas and destruction of interlobular bile ducts ✓ AMA-negative, but ANA and ASMA may be present
Primary sclerosing cholangitis[8]	✓ Cholestatic biochemical profile ✓ Cholangiography endoscopic retrograde cholangiography shows characteristic bile duct changes with multifocal strictures and segmental dilatations ✓ Secondary causes of sclerosing cholangitis excluded ✓ Patients who present with clinical, biochemical, and histologic features compatible with PSC, but have a normal cholangiogram, were classified as small-duct PSC
Overlap syndrome AIH/PBC[10]	AIH (2 out of 3 criteria) (1) Alanine aminotransferase levels $>5\times$ ULN (2) Serum immunoglobulin G levels $>2\times$ ULN or a positive test for ASMA (3) Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis PBC (2 out of 3 criteria) PBC (2 out of 3 criteria) (1) Alkaline phosphatase levels $>2\times$ or γ-glutamyltranspeptidase levels $>5\times$ ULN (2) Positive test for AMA (3) Liver biopsy specimen showing florid bile duct lesions
Autoimmune hepatitis[9]	Simplified International Autoimmune Hepatitis Criteria Group 2008

AIH = autoimmune hepatitis; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = antismooth muscle antibody; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; ULN = upper limit of normal.