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Characteristics of autoimmune hepatitis in a sample of Egyptian children

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ABSTRACT

Background: Autoimmune hepatitis is a rare liver disease that can be presented aggressively in children. Early treatment can control the hyper immune state and save the liver.

The aim of the work: To assess clinical manifestations, biochemical features, and response to immunosuppressive drugs in children with AIH.

Methods: 25 children with AIH, based on the International Scoring Criteria of Autoimmune Hepatitis (*IAIHG score system*), recruited from Pediatric Hepatology clinic, Benha University Hospitals have been analyzed for their clinical, biochemical features, histological profile and their response to treatment.

Results: 25 children were 15 female (60%) and 10 male (40%) their ages ranged from 3 to 15 years old. The main clinical presentation were jaundice (68.0%), abdominal pain (48.0%), acute hepatic-like illness was the first presentation in (32.0%), hepatomegaly (80.0%), splenomegaly (40.0%) lower limb edema (12.0%), and ascites (12.0%). All patients at first presentations had high serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum immunoglobulin G (IgG). According to the autoantibody profile, all children were classified as AIH type 1 as no patient was seropositive for anti-liver kidney microsome antibody (anti-LKM). Prednisone with or without azathioprine was started and complete remission noticed in 13 (52.0%) while 12 (48.0%) had relapses.

Conclusion: AIH type 1 was the main type of autoimmune hepatitis in children referred to Benha University Hospitals. Females more affected than boys. The combination of prednisone and azathioprine are effective in abating the inflammatory process in most of the cases. Early diagnosis and treatment of AIH had apparently good outcome in children.

Introduction

Autoimmune hepatitis (AIH) is a disease characterized by effective therapeutic intervention including corticosteroid treatment was proved to be convincing in most of the cases. However, 50 years later it remains a major diagnostic and therapeutic challenge because two major reasons: First; it is a relatively rare disease. Second, AIH is a very heterogeneous disease.[1]

AIH affects patients who have lost immune tolerance to autologous liver antigens. Serologically characterized by elevated liver enzymes, immunoglobulin G (IgG), the presence of autoantibodies and histologically characterized by interface hepatitis in the absence of a known etiology. It is predominate in females.[2]

AIH can be classified into two types according to profile of auto antibody: AIH type 1 are positive for antinuclear antibody (ANA) and/or anti-smooth muscle antibody (ASM), AIH type 2 are positive for anti-liver-kidney–microsomal antibody type1 (Anti-LKM-1).[3]

AIH Patients may have acute, fulminant, or asymptomatic presentations. They may lack conventional serological markers and have atypical histological features, so autoimmune hepatitis must be considered in all patients with acute and chronic hepatitis of undetermined cause, including patients with graft dysfunction after liver transplantation.[4]

Treatment with Prednisone or prednisolone in combination with azathioprine is the preferred treatment, as use, these medications in various doses can ameliorate treatment failure, incomplete response, drug intolerance, and relapse after drug withdrawal.[5]

There are two sets of diagnostic criteria used to standardize the diagnosis of AIH. International Autoimmune Hepatitis Group (IAIHG), scores of 10–15 before treatment corresponds to a diagnosis of "probable" AIH and >15 before treatment corresponds to a diagnosis of definite AIH, and when the outcome of treatment is included, the corresponding values are 12–17 and >17 respectively.[6] Because these criteria are complex, the IAIHG developed

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a simplified scoring system (Table 1) based on four components and twelve possible grades. The included parameters were represented by autoantibody titer, IgG levels, liver histology, and exclusion of viral hepatitis. A Score of ≥6 (8 being maximum) equates to probable "AIH" whereas a score of ≥7 denotes "definite AIH".[7] With this as a background, we aimed to assess clinical manifestations, biochemical features, and response to immunosuppressive drugs in children with AIH attained to pediatric hepatology clinic, Benha University Hospitals.

Patients and methods

This retrospective study included 25 children with AIH out of 7842 patients with hepatitis (0.3%) referred to Pediatric Hepatology clinic, Benha University Hospitals, between January 2004 and January 2017. The diagnosis of AIH was made according to the diagnostic criteria defined by International Autoimmune Hepatitis Group[8]: (1) a raised IgG level and presence of organ-specific and non-organ-specific autoantibodies; (2) presence of interface hepatitis and portal plasma cell infiltration on liver histology; (3) the absence of other liver diseases of known etiology. AIH was classified into two subtypes according to seropositivity for autoantibodies: patients with the presence of antinuclear antibodies (ANA, titer ≥ 1:20) and/or anti-smooth muscle antibodies (anti-SMA, tit er ≥ 1:20) were classified as having AIH1 and those with the presence of liver-kidney-microsomal type 1 antibody (LKM1, titer ≥ 1: 10) as having AIH2 [8].

Exclusion criteria: Viral hepatitis, drug induced hepatitis, Fatty liver disease and metabolic disorders.

Being a retrospective study, a written informed consent was not needed. The study was approved by the Ethical Scientific Committee of Benha University and was carried out according to the guidelines of the Helsinki Declaration.[9]

Methodology

All the following data were collected from the files of the patients that include: demographic data, presenting clinical features, clinical examination, biochemical parameters, histological and radiological findings, treatment response and outcome:

Biochemical parameters included:

- Liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, alkaline phosphatase, total and direct bilirubin, serum protein, serum albumin, prothrombin time (PT)]: using Biosystem A15 auto-analyzer by appropriate chemical principles.
- Complete blood count: using automated hematology system, (Sysmex XE 5000).
- Serum immunoglobulin G concentration (IgG): by radial immunodiffusion (IgG – NL RID, RN004.3, Binding Site, Birmingham, UK).
- Quantitative and qualitative determination of antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA) and antibodies to liver-kidney-microsome type 1 (anti-LKM-1): by indirect immunofluorescence technique using NOVA Lite® Rat Liver, Kidney, Stomach (INOVA Diagnostics, Inc, Germany).

- **To exclude other cause of liver diseases, all the patients were subjected to the following before taking liver biopsy:**

1. Serological tests for viral hepatitis A, B and C, cytomegalovirus IgM as well as Epstein-Barr virus (EBNA IgM and VCA IgM).
2. Work up for Wilson's disease (serum ceruloplasmin, 24-h urinary copper before and after penicillamine, Keyser-Fleischer rings).
3. Alpha-1-antitrypsin deficiency was excluded by the absence of characteristic clinical features and negative PAS stain in liver biopsy.

- **Abdominal ultrasonography** for assessment of liver (span and texture), spleen span and presence of ascites.
- **Liver biopsy was performed for all cases**

Ultrasound-guided liver biopsy was done for all patients using a Tru-Cut needle (Hepafix luer Lock, Braun Melsungen AG, 3409 Melsungen, Germany). A core of liver tissue containing at least 5 portal tracts was considered sufficient. Biopsy specimens were fixed in formalin and embedded in paraffin. Five-μm thick sections were cut, mounted on a glass slide and stained with Hematoxylin and Eosin to evaluate pathological changes, with Mason-Trichrome that stains collagen fibers to assess fibrosis, and with Perls' Prussian blue stain which reveals iron deposits. PAS stain to exclude Alpha-1-antitrypsin deficiency. Hepatitis activity index (HAI) and fibrosis stage are two important results during the assessment of liver samples that determine the mild, moderate or the severity of the disease. HAI scores ranging from 0 to 18, the total activity scores are defined as follows: (1–3, minimal; 4–8, mild; 9–12, moderate; 13–18, severe) (Table 2). The scores of fibrosis are defined as follows: (0, no fibrosis; 1, fibrous expansion of some portal areas, with or without short fibrous septa; 2, fibrous expansion of most portal areas, with or without short fibrous septa; 3, fibrous expansion of most portal areas with occasional portal to portal bridging; 4, fibrous expansion of most portal areas with marked bridging (portal to portal as well as portal to central); 5, marked bridging with occasional nodules (incomplete cirrhosis); 6, cirrhosis, probable or definite).[10]

All patients were initially treated with prednisolone (2 mg/kg/-day; maximum 60 mg/day). This was gradually tapered by 5 mg every 1–2 weeks depending upon the clinical symptoms and AST and ALT activity. A maintenance dose of 10 mg prednisolone continued for two years after improvement. Azathioprine (1–2 mg/kg/-day; maximum 100 mg/day) was administered with prednisolone if an increase in AST or ALT level was observed on tapering the dose of steroid or appearance of significant side effects that necessitate reducing the dose of steroid (like severe cosmetic changes or duodenal ulcer or hypertension or corticosteroid-related osteopenia detected by bone densitometry). Significant side effects of azathioprine were thrombocytopenia and leucopenia. All patients were followed up after the end of treatment throughout the period of the study.

Table 1
Simplified criteria for the diagnosis of autoimmune hepatitis.[7]

Feature/parameter	Score
ANA or ASMA titers ≥ 1:40 by IIF	+1
ANA or ASMA titers ≥ 1:80 by IIF	+2
or LKM ≥ 1:40 by IIF	+2
or SLA/LP positive	+2
IgG-levels > UNL	+1
IgG levels > times 1.10 UNL (>1.1 times ULN)	+2
Liver histology atypical for AIH	0
Liver histology compatible for AIH	+1
Liver histology typical for AIH	+2
Exclusion of viral hepatitis: IgM anti-HAV, HBsAg, HBV DNA, HCV RNA	+2

Definite autoimmune hepatitis: ≥7, Probable autoimmune hepatitis: ≥6.
ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, antibodies to liver kidney microsome type 1; SLA, soluble liver antigen; IIF, indirect immunofluorescence; ULN, upper limit of the normal range; IgM, immunoglobulin M; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; HCV, hepatitis C virus; RNA, ribonucleic acid.