INTRODUCTION

Autoimmune hepatitis is a chronic disease of unknown cause, characterized by continuing hepatocellular inflammation and necrosis and tendency to progress to cirrhosis. It is prevalent in children and adults with female predominance and variable clinical presentations ***(Decock et al., 2009)***.

Immune serum markers are frequently present in autoimmune hepatitis. The disease is often associated with other autoimmune diseases ***(Krawitt, 2006)***.

Prednisone, with or without 6-mercaptopurine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease ***(Czaja et al., 2005)***.

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. In patients meeting the criteria for tapering and then withdrawal of treatment (25-40% of children), 50% are weaned from all medication; in the other 50%, relapse occurs after a variable period. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone that minimizes biochemical activity of the disease. Continual screening for

complications of medical therapy (ophthalmologic examination, bone density measurement, blood pressure monitoring) is recommended ***(Decock et al., 2009)***.

Predictors of response to immunosuppressants include, Age of onset of the disease, decompensated cirrhosis at presentation, other coexistent autoimmune disease, Acute hepatitis at presentation, cholestasis at presentation, disease onset during pregnancy, Fulminant forms of AIH have high mortality in untransplanted patients ***(Floreani et al., 2006)***.

AIM OF THE WORK

Our aim was to define the demographic, biochemical and histological characters of our patients with AIH and to determine predictors of treatment response.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disorder affecting mainly females, characterized serologically by high levels of transaminases and immunoglobulin G (IgG), and presence of autoantibodies. Histologically it is characterized by interface hepatitis, in the absence of a known etiology ***(Vergani et al., 2007)***.

Onset is frequently insidious with nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain, and arthralgia at presentation, but the clinical spectrum is wide, ranging from an asymptomatic presentation to an acute severe disease ***(Czaja, 2005 and Ichai et al., 2007).***

In one Egyptian study, children with AIH were (68%) females and (32%) males, their ages ranged from 6 to 18 years with a mean age of 13.2 ± 3.8 years. The mean duration of illness was 4.4 ± 3.1 years ***(Khalil et al., 2000)***.

Historical background:

In 1950, Waldenstrom first described a form of chronic hepatitis in young women. This condition was characterized by cirrhosis, plasma cell infiltration of the liver, and marked hypergammaglobulinemia ***(Waldenstrom, 1950)***.

Kunkel, in 1950, and Bearn, in 1956, described other features of the disease, including hepato-splenomegaly,

jaundice, acne, hirsutism, cushingoid facies, pigmented abdominal striae, obesity, arthritis, and amenorrhea ***(Kunkel et al., 1950 and Bearn et al., 1956)***.

In 1955, Joske first reported the association of the lupus erythematosus (LE) cell phenomenon in active chronic viral hepatitis ***(Joske et al., 1955)***.

This association led to the introduction of the term lupoid hepatitis by Mackay and associates in 1956 ***(Cowling et al., 1956)***.

Researchers currently know that no direct link exists between systemic lupus erythematosis (SLE) syndrome and autoimmune hepatitis; patients with systemic lupus erythematosis do not have an increased incidence of autoimmune hepatitis and the two diseases are distinct entities, thus, lupoid hepatitis is not associated with SLE ***(Krawitt, 1996)***.

The development of viral serologic tests represented another important step forward. These permitted hepatologists to differentiate chronic viral hepatitis from other types of chronic liver disease, including autoimmune hepatitis. The histopathologic description of autoimmune hepatitis has undergone several revisions over the years. In 1992, an international panel codified the diagnostic criteria.The term autoimmune hepatitis was selected to replace terms such as autoimmune liver disease and autoimmune chronic active

hepatitis. The panel waived the requirement of 6 months of disease activity to establish chronicity, expanded the histologic spectrum to include lobular hepatitis, and reaffirmed the non viral nature of the disease. The panel also designated incompatible histologic features, such as cholestatic histology, the presence of bile duct injury, and ductopenia ***(Johnson et al., 1993)***.

Epidemiology:

Based on limited epidemiologic data, the prevalence of AIH is estimated to range between 0.1 and 1.2cases per 100,000 in Western Europe and North America among the white population but only 0.08–0.015 cases per 100,000 in Japan ***(Nishioka et al., 1998)***.

In the North American and Western European white population, AIH accounts for about 20% of chronic hepatitis cases, and in Brazil only 5%–10% of patients with chronic hepatitis suffer from AIH ***(Cancado et al., 2000)***.

Racial, sexual, and age-related differences in incidence:

The disease is most common in whites of northern European ancestry with a high frequency of HLA-DR3 and HLA-DR4 markers. The Japanese population has a low frequency of HLA-DR3 markers. In Japan, autoimmune hepatitis is associated with HLA-DR4 ***(Czaja, 2009)***.

Women are affected more frequently than men (sex ratio, 3.6:1) ***(Gregorio et al., 1997)***.

Autoimmune hepatitis has a bimodal age distribution, with a first peak of incidence at age 10-20 years and a second at age 45-70 years. Approximately one half of affected individuals are younger than 20 years; incidence peaks in premenstrual girls. Patients with AIH-2 tend to be younger; 80% of patients with AIH-2 are children. However, autoimmune hepatitis may occur in people of any age, including infants and older adults ***(Czaja, 2009 and Mieli-Vergani et al., 2009 and Haider et al., 2009)***.

Pathophysiology:

Early studies have shown that patients with AIH have impaired 'suppressor' cell function, which could be corrected following in vitro exposure to therapeutical doses of steroids Later on a defect specifically involving a subpopulation of T-lymphocytes controlling immune responses directed against a liver-specific membrane autoantigen was reported In line with these observations, evidence provided over the last five years has indicated that an impairment in regulatory T-cells is key to the loss of immune tolerance in AIH and to the emergence of uncontrolled effector autoimmune responses ***(Longhi et al., 2006)***.

AIH is a complex polygenic disorder unlikely to be transmitted to subsequent generations; thus, routine screening of patients or family members for genetic markers is not recommended ***(Czaja, 2008)***.

Genetic predisposition:

Genetic susceptibility to developing autoimmune hepatitis has been associated with the HLA haplotypes B8, B14, DR3, DR4, and Dw3. Also *C4A* gene deletions are associated with the development of autoimmune hepatitis in younger patients ***(Scully et al., 1993)***.

AIH may be present in patients with multiple endocrine organ failure, mucocutaneous candidiasis, and ectodermal dystrophy. Such patients have the autosomal recessive genetic disorder autoimmune polyendocrinopathy candidiasis, ectodermal dystrophy (APECED). Auto-antigens associated with APECED are cytochrome P450 1A2 (CYP1A2), CYP2A6 in addition to CYP2D6 ***(Aaltonen et al., 1994)***.

Antibodies to cytochrome P450 1A2 were previously called anti liver microsomal (anti-LM) antibodies. This is the only syndrome involving AIH that exhibits a Mendelian pattern of inheritance, and genetic counseling for the patient and family members are warranted ***(Obermayer et al., 2001 and Choudhuri et al., 1998)***.

HLA-DR3–positive patients are more likely than other patients to have aggressive disease, which is less responsive to medical therapy and more often results in liver transplantation; in addition, these patients are younger than other patients at the time of their initial presentation. HLA-DR4–positive patients are more likely to develop extrahepatic manifestations of their disease ***(Czaja, 1993)***.

In one Egyptian study, the most frequent alleles found in Egyptian children with AIH were HLA-DRB1*13 (36%), HLA-DRB1*04 (18%) and HLA-DRB1*03 (14%). In type I AIH patients HLA-DRB1*13 was the most frequent allele (32.4%), followed by HLA-DRB1*04 in (20.6%) and HLA-DRB1*03 in (14.7%), While in type II, the most frequent alleles were HLA-DRB1*13 in (40%), HLA-DRB1*07 (20%) and HLA-DRB1*15 in (20%). HLA-DRB1*12 was significantly more frequent in AIH patients positive for Hepatitis A IgM than in patients negative for hepatitis A IgM. There was no statistically significant difference between partial responders and complete responders to treatment as regards HLA-DRB1 subtypes ***(Elfaramawy et al., 2010)***.

Environmental triggers:

The environmental agents assumed to induce autoimmune hepatitis have not been delineated but may include viruses. The finding of molecular mimicry by cross-reactivity between epitopes of viruses and certain liver antigens adds

credence to a hypothesis of virally triggered disease. Because the trigger or triggers of autoimmune hepatitis may be part of a so-called hit-and-run phenomenon, in which induction occurs many years before overt autoimmune disease, identifying an infectious agent may prove impossible. There has been evidence implicating measles virus, hepatitis viruses, cytomegalovirus, and Epstein–Barr virus as initiators of the disease; the most convincing evidence is related to hepatitis viruses ***(Singh et al., 2007 and Vento et al., 2004)***.

Some bacteria were also incriminated. Casswall et al., isolated *helicobacter* species DNA in 50% of liver biopsies from their patients with autoimmune hepatitis and ulcerative colitis ***(Casswall et al., 2010)***.

Certain drugs, including oxyphenisatin, methyldopa, nitrofurantoin, diclofenac, interferon, pemoline, minocycline, and atorvastatin, can induce hepatocellular injury that mimics autoimmune hepatitis. It has also been suggested that herbal agents such as black cohosh and dai-saiko-to might trigger autoimmune hepatitis. Whether drugs and herbs unmask or induce autoimmune hepatitis or simply cause drug induced hepatitis with accompanying autoimmune features is unclear ***(Graziadei et al., 2003)***.

Figure (1): Black cohosh

Is a flowering plant, it is native to eastern north America, extracts from this plant are thought to possess analgesic, sedative and anti inflammatory properties ***(Predny et al., 2009)***.

Today extracts are being studied as effective treatment for symptoms associated with menopause. (it acts like estrogen) ***(Beer et al., 2013)***.

Side effects:

1- May be thickening of womb lining that increases the risk of womb cancer.

2- It can damage the liver in patients with liver problems.

Although several well controlled clinical trials found no evidence that black cohos preparations have any adverse effect on the liver function. Australia added a warning to the label of all black cohos preparartions stating that it may cause harm to the liver in some individuals and should not be used without medical supervision ***(Naser et al., 2011)***.

Figure (2): Dai-saiko-to

Is a Japanese herbal medicine:

There are studies on its effect on decreasing plasma lipids and atherosclerotic lesions ***(Mizuno et al. 2008)***.

Pathogenesis:

The etiology of AIH is unknown, although both genetic and environmental factors are involved in its expression ***(Czaja and Donaldson, 2000)***.

The HLA-DR3 and HLA-DR4 genes of the major histocompatibility complex have been implicated as genetic predisposing factors.The major genetic determinant for children with AIH-1 is HLA-DRB1, while AIH-2 is associated with the HLA-DQB1 gene. Strong evidence suggests that defects in immunologic control of auto reactivity play a role in AIH pathogenesis ***(Djilali et al., 2004)***.

Patients with AIH have low levels of T lymphocytes that express the CD8 marker and a specific defect in a subpopulation of T cells that controls the immune response to specific liver cell membrane antigens. A genetically determined partial C4 deficiency has been reported. C4 has a well-known role in virus neutralization; failure to eliminate viruses may lead to immune reaction against antigen on infected cells. Among the several viruses implicated as triggering agents are rubella, Epstein-Barr, and hepatitis A, B, and C. Some authors have shown a high amino acid sequence homology between hepatitis C virus (HCV) polyprotein and CYP2D6, the molecular target of LKM-1 antibody, which suggests that molecular mimicry may trigger production of LKM-1 antibody in HCV infection ***(Longhi et al., 2009)***.

Autoimmune attack to the liver cell. (Figure3)

A specific autoantigenic peptide is presented to an uncommitted T-helper (TH0) lymphocyte within the HLA class II molecule of an antigen presenting cell (APC). TH0 cells

become activated and, according to the presence in the microenvironment of interleukin (IL)-12 or IL-4 and the nature of the antigen, differentiate into TH1 or TH2 and initiate a series of immune reactions determined by the cytokines they produce: TH1 secrete IL-2 and interferon-gamma (IFN-g), which stimulate cytotoxic T-lymphocytes (CTL), enhance expression of class I and induce expression of class II HLA molecules on hepatocytes and activate macrophages; activated macrophages release IL-1 and tumour necrosis factor alpha (TNF-a). TH2 secrete mainly IL-4, IL-10 and IL-13, and direct autoantibody production by B-lymphocytes. If regulatory T-cells (Tr) do not oppose, a variety of effector mechanisms are triggered: liver cell destruction could derive from the action of CTL; cytokines released by TH1 and recruited macrophages; complement activation or engagement of Fc receptor-bearing cells such as natural killer (NK) lymphocytes by the autoantibody bound to the hepatocyte surface ***(Lobo-Yeo and Senaldi, 1991)***.

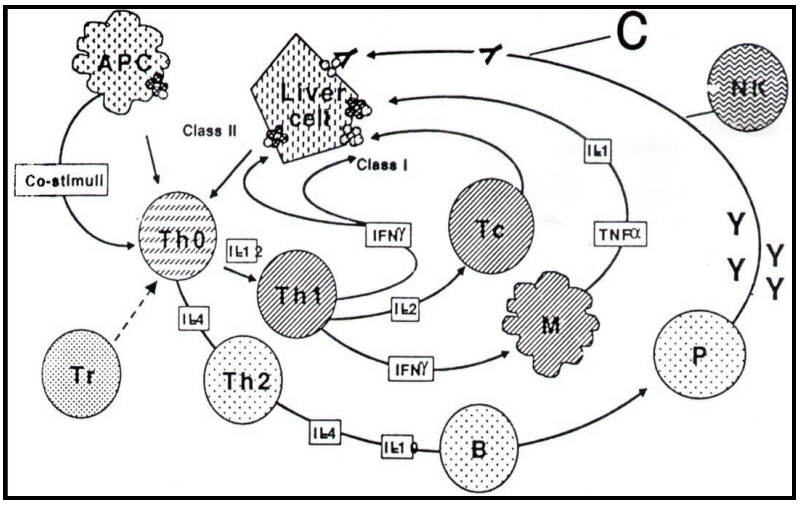

Figure (3): The possible pathways that an immune attack can follow to inflict damage on the hepatocyte

Classification (Table 1)

A key criterion for the diagnosis of AIH is the detection of anti nuclear antibody (ANA), smooth muscle antibody (SMA) and anti liver kidney macrosome 1 (anti-LKM-1) by indirect immunoflurescence. Autoantibody detection not only assists in the diagnosis but also allows differentiation of AIH in type 1 and type 2.ANA and SMA and anti-LKM-1 are practically mutually exclusive; in those instances when they are present simultaneously, the child is classified having AIH type 2 ***(Vergani et al., 2004).***